FORMULATION AND EVALUATION OF TRIPLE DRUG COMBINATION OF OLMESARTAN MEDOXIMIL, AMLODIPINE BESYLATE AND HYDROCHLORTHIAZIDE TABLETS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

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IN

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Submitted by

Register Number: 26111005

UNDER THE GUIDANCE

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CERTIFICATE

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DECLARATION

I hereby declare that the thesis entitled **"FORMULATION AND EVALUATION OF TRIPLE DRUG COMBINATION OF OLMESARTAN MEDOXIMIL, AMLODIPINE BESYLATE AND HYDROCHLORTHIAZIDE TABLETS"** has been originally carried out by me under the supervision and guidance of Mr**. V. Prabhakaran, M. Pharm.,** (Industrial guide), **Dr. U. Ubaidulla, M. Pharm., Ph.D.,** (Institutional Guide) , Department of Pharmaceutics, C.L.Baid Metha college of Pharmacy, Chennai-97, during the academic year 2012-2013.

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ABBREVIATIONS

API	Active pharmaceutical Ingredient
HPMC	Hydroxy propyl methyl cellulose
IPA	Iso Propyl Alcohol
HPLC	High performance liquid chromatography
FTIR	Fourier transformer infrared spectroscopy
RH	Relative Humidity
USP	United States Pharmacopoeia
IP	Indian Pharmacopoeia
CI	Compressibility Index
HR	Hausner Ratio
WHO	World Health Organisation
IR	Immediate Release
DDS	Drug Delivery System
GI	Gastro Intestinal Tract
CCB	Calcium Channel Blocker
ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
AR	Analytical Reagent
RPM	Rotation Per Minute
FBD	Fluidized Bed Dryer
ICH	International Conference on Harmonisation

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Sec	Seconds
Hr	Hour
SD	Standard Deviation

CONTENTS

INTRODUCTION

1.0 INTRODUCTION:

The oral route of drug administration is the most important method of administering drugs for systemic effects. Of drugs that are administered orally, solid oral dosage form represents the preferred class of products.

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known as solid unit dosage forms. Tablets represent unit dosage form in which one usual dose of the drug has been accurately placed.[1]

Tablet may be defined as solid pharmaceutical dosage forms containing drug substance with or without suitable diluents and have been traditionally prepared either by compression or molding methods.

Frequently, tablets are discoid in shape; they are also round, oval, oblong, cylindrical or triangular. They differ greatly in size and weight depending on the amount of drug substance present and intended method of administration.[2]

Tables are obtained by compression of uniform volumes of powders or granules by applying high pressure and using punches and dies. The particles to be compressed consist of one or more medicaments, with or without auxiliary substance such as diluents, binders, and disintegration agents, lubricant, glide ants and substances capable of modifying the behaviour of the medicaments in the digestive tracts. Such substances must be innocuous and therapeutically inert in the quantities present.

Due to emergence of precompression, induced die feeding, high -speed, ultrahigh-speed presses, automated weight-control systems, the availability of many new direct compression materials, and the microprocessor control of precompression, compression and ejection forces the formulation of solid oral dosage forms, especially tablets has undergone rapid changes and development.[3]

1.1 PROPERTIES OF TABLETS[4]:

The characteristics of an acceptable tablet are as follows:

1. The hardness and friability tests are the two tests that are conducted in order to understand the strength and resistance of the tablet which determine the strength towards shock and abrasion which may occur during manufacturing, packing, shipping and use.

2. The drug content and weight of the tablets should be uniform individually. The weight variation test and the content uniformity test are performed to attain this consistency.

3. The drug content of the tablet must be bioavailable. This property is also measured by two tests, the disintegration test and the dissolution test. However, bioavailability of a drug from a tablet, or other dosage form, is a very complex problem and the results of these two tests do not provide an index of bioavailability. This must be done by blood levels of the drug.

4. Tablets must be aesthetic in appearance and must have the featured shape, colour, and other shape necessities to identify the product. The monogram or logo of the manufacturer is a must.

5. Tablets must retain all of their function, which include drug stability and efficacy.

1.2 The advantages of the Tablet dosage form[5]:

1. They come in single units.
2. They offer the greatest capabilities of all oral dosage form for the best dose precision.
3. Of all oral dosage forms, Cost is the lowest.
4. Lighter and compact.
5. Easiest and cheapest to be packed as strips.
6. Easy to swallow.
7. Enteric coating helps in delayed release.
8. Coating technique can be used to prevent objectionable odor and bitter taste.
9. Large scale production is easy.

10. Best chemical and microbial stability over all oral dosage form.
11. Monogrammed punch helps in easy product identification requiring no additional steps.

1.3 Disadvantages of tablet dosage form[6]:

1. Children and unconscious patients feel it hard to take.
2. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
3. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
4. Bitter and objectionable odor tablets are hard to intake which may require coating techniques which in turn reflect in the cost of the tablets making it costly.

1.4 Oral Drug Delivery[7]:

Oral drug delivery systems are divided into 3 categories, based on the desired therapeutic objectives.

I. Immediate-release preparations,

II. Controlled-release preparations and

III. Targeted- release preparations.

1.4.1 Immediate-Release Preparations

These preparations are intended primarily to achieve faster onset of action Advantages of immediate release preparations include

- Enhanced oral bioavailability through transmucosal delivery and pregastric absorption
- Convenience in drug administration to dysphasic patients.

Conventional IR formulations include granules and fast disintegrating tablets that use effervescent mixtures, such as sodium carbonate sodium bicarbonate, citric

acid, tartaric acid and superdisintegrants such as sodium starch glycolate, croscarmellose sodium, and crospovidone.

In fast-dispersing dosage forms, current technologies include modified tableting systems, floss or Shear form technology. They employ application of controlled temperature, freeze-drying and centrifugal force.

1.4.2 Controlled-Release Preparations:

The current controlled release technologies for oral drug delivery include diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems are monolithic and reservoir devices. In this diffusion of the drug is the rate-limiting step, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by swelling of polymer.

Release of drugs from chemically controlled systems is through degradation of polymer (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. Programmed-release (‘‘tailored-release’’) profile of a final CR product is the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. In terms of appropriate selection of polymers and excipients that incorporate desired principles, makes it simple.

1.4.3 Targeted-Release Preparations:

Site-specific release oral drug delivery requires spatial placement of a drug delivery device at a desired site within the GI tract. Though it is possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is easy compared to that in the stomach and the small and large intestines. Consideration of both longitudinal and transverse aspects of GI constraints is necessary for small, large intestine and stomach.

1.5 Stages in manufacturing of tablets[8]:

Tablets are manufactured by forcing powder particles into close proximity to each other by powder compression. This enables the particles to cohere into a

porous, solid specimen of defined geometry. The compression takes place in a die by the action of two punches,

- The lower and
- The upper, by which the compressive force is applied.

Powder compression is defined as the reduction in volume of the powder owing to the application of the force. Increased proximity of the particle surface is accomplished during compression because of which bonds are formed between the particles. This provide coherence to the powder, a compact is formed. Compaction is defined as the formation of a solid mass of defined geometry by powder compression.

The process of tableting is divided into three stages.

1.5.1 Die-filling:

This step involves the gravitational flow of the powder from a hopper through the die table into the die. The die is closed at its lower end by the lower punch.

1.5.2 Tablet formation:

The upper punch descends down and enters the die. The powder is then compressed until a tablet is formed. The lower punch can be a stationary or can move upwards in the die during the compression phase. After application of maximum force, the upper punch leaves the powder and ascends up, which is the decompression phase.

1.5.3 Tablet ejection:

During this phase, the lower punch rises up until its up reaches the level of the top of the die. The tablet is subsequently removed from the die subsequently.

1.6 TYPES OF TABLET MANUFACTURING[9]:

The tablet manufacturing process can be broadly classified as

- Granulation
- Direct compression

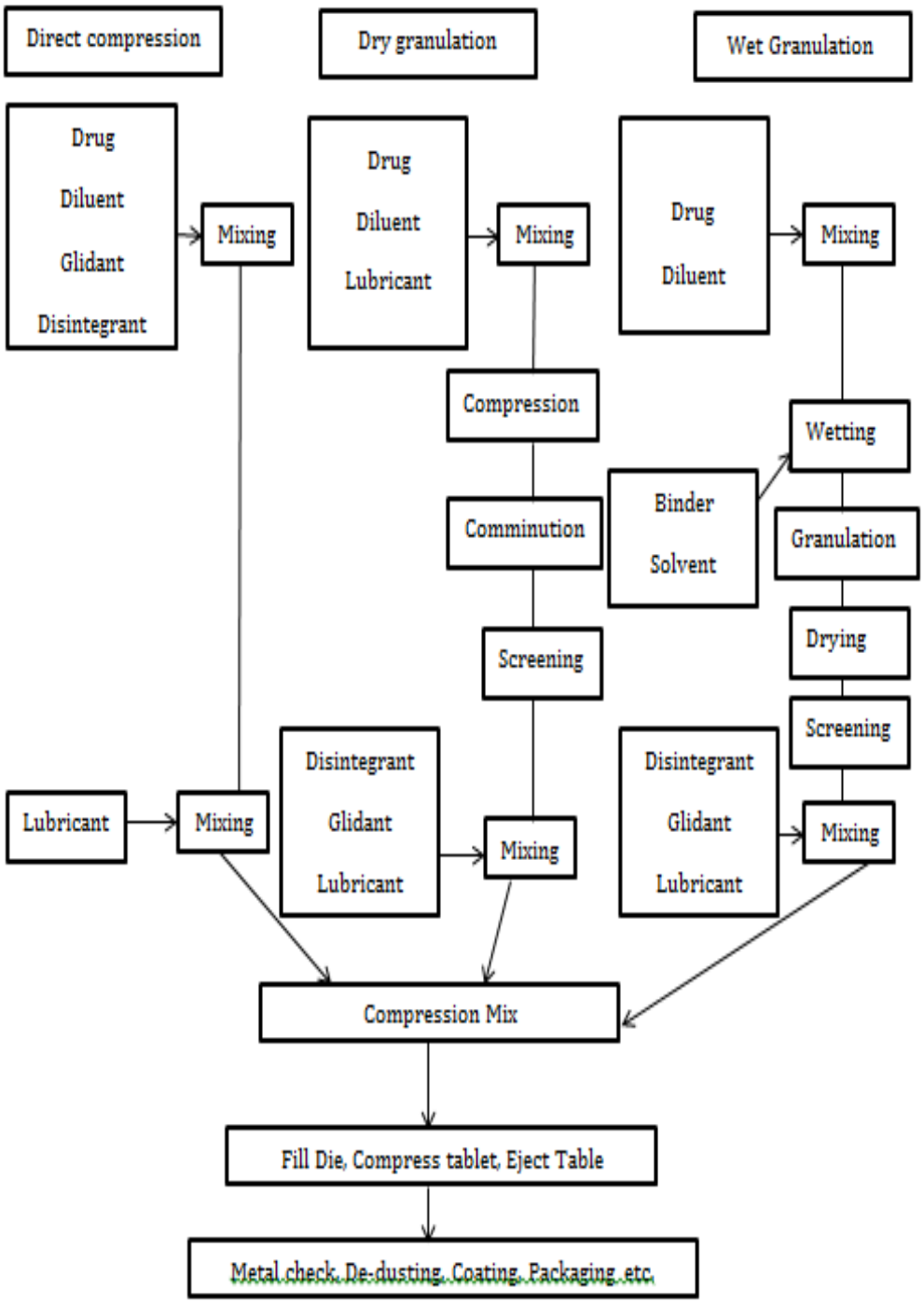


Figure 1: Tablet manufacturing processes

1.6.1 Granulation:

1.6.1.1 Wet granulation:

For powders which are very fine, fluffy, will not stay blended, or will not compress, granulation is preferred. Wet granulation involves addition of solution to blended powder and mixing is done at a predetermined period of time and at specified speed. After this process is complete, the wet mass is milled and dried on a tray drier on to which the mass is spread.

1.6.1.2 Dry granulation:

Dry granulation (roll compaction or slugging) involves the compaction of powders at high pressures into large, often poorly formed tablets or compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of heat and moisture in the processing. Dry granulations can be produced by extruding powders between hydraulically-operated rollers to produce thin cakes that are subsequently screened or milled to give the desired granule size.

1.6.2 Direct compression:

Direct compression is used when a group of ingredients are to be blended and placed onto a tablet press to be made into a perfect tablet without changing any of the ingredients. Powders that can be blended and compressed are commonly referred to as directly compressible or as direct-blend formulations.

The physical properties of the individual filler materials are highly critical, and minor variations in properties can alter flow and compression characteristics which make them unsuitable for direct compression.

The most widely used direct compression fillers include cellulose derivatives (e.g. microcrystalline cellulose), saccharides (e.g. lactose and mannitol), mineral salts (e.g. Dicalcium phosphate, calcium carbonate) and partially pregelatinized starch.

TABLE 1: Advantages and Disadvantages of methods of manufacturing.

Method	Advantage	Disadvantages
Direct compression	• It is Simple, economical process • No heat or moisture is associated, so good for unstable compounds.	• It is not suitable for all kinds of API • It is generally limited to lower dose compounds, Segregation potential, expensive excipients
Wet Granulation	• It is a robust process • It reduce elasticity problems and wettablity, • Reduced segregation potential.	• It is an expensive process, • It is time and energy consuming, • Specialized equipments are required • Stability issues.
Wet Granulation(Non Aqueous)	• Because of the Vacuum drying technique, it is suitable for moisture sensitive API	• Expensive equipment, • solvent recovery issues, • Needs organic facility, health and environmental issues.
Dry Granulation	• It eliminates exposure to moisture and drying	• Dusty procedure, • slow process, • not applicable for all API

1.7 TYPES OF TABLETS[10]:

The various types of tablets include,

1. Compressed tablet
2. Sugar coated tablet
3. Film coated tablet
4. Enteric coated tablet
5. Multi compressed tablet

1.7.1 Compressed tablet:

These tablets are formed by compression and they do not have any coating. They are made from powdered, crystalline or granular materials alone or in combination with binders, disintegrants, controlled release polymers, lubricants, diluents and colorants.

1.7.2 Sugar coated tablets:

These are compressed tablets surrounded by sugar coating. Coating may be colored and used in covering drug substances possessing objectionable color and odor.

1.7.3 Film coated tablets:

These are compressed tablets covered with a thin layer or film of a water soluble material. Polymers with film forming properties are used. It shows the same characters as that of sugar coated tablets. It has an advantage of reduced time period for coating.

1.7.4 Enteric coated tablets:

These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in intestine. This coating is used for tablet containing drug substances that are inactivated or destroyed in stomach, those that irritate the mucosa, or as a means of delayed release of medication.

1.7.5 Multi compressed tablets:

These are compressed tablets made by more than one compression cycle. This is used when separation of active ingredient is needed for stability purpose or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients.

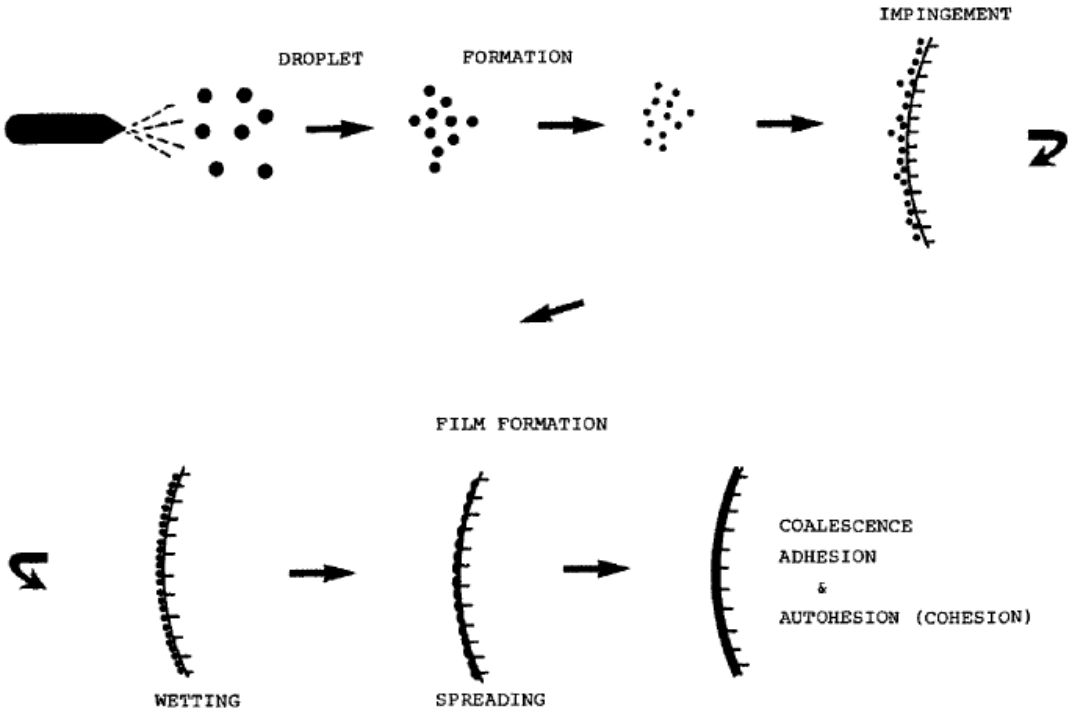
1.8 FILM COATING OF SOLID DOSAGE FORMS[11]:

Film coating is a process that involves deposition of thin, uniform film onto the surface of the substrate. Unlike sugar coating, this is a very flexible process that allows a broad range of products like tablets, granules, non pareils, and capsules to be coated. Film coating are applied continuous to a moving mass of product, usually by means of a spray technique, all though manual application procedures have been used.

Advantages of film coating include:

a) Minimal weight increase (typically 2%-3% tablet core weight)
b) Significant reduction in processing times
c) Increased process efficiency and output
d) Increased flexibility in formulations
e) Improved resistance to chipping of the coating

Figure 2: schematic representation of film coating process



Raw materials used in film coating:

The major component in any film coating formulation consists of polymer, plasticizer, colorant and solvent. Ideal properties for the polymer include solubility in a wide range of solvent systems to promote flexibility in formulation , an ability to produce coating that have suitable mechanical properties and appropriate solubility in gastrointestinal fluids such that drug bioavailability is not compromised.

Cellulose ethers are often the preferred polymers in film coating, particularly hydroxyl propyl methyl cellulose. Suitable substitutes include hydroxyl propyl

cellulose, which may produce slightly tackier coatings and methyl cellulose which retard drug dissolution.

1.9 EXCIPIENTS USED IN FORMULATION[12]:

Oral conventional dosage form contains some components other than active pharmaceutical ingredients which are functioning as diluents, binder or adhesive, disintegrant, lubricant, colorants, flavors and sweeteners.

1.9.1 Diluents:

These are the fillers used to make up the bulk of the tablet when the drug dosage form is insufficient to produce the bulk. In some drugs, the dose is high such that no filler is required.

Diluents and other excipients must meet the following criteria:

- They must be nontoxic and acceptable to the regulatory agencies in all countries where the product is to be marketed.
- Cost must be acceptably low.
- They should not be contraindicated by themselves.
- They should be commercially available in all countries where the product is to be manufactured.
- They must be inert physiologically inert.
- They must be stable physically and chemically by themselves and in combination with the drug and other tablet components.
- They must be color compatible.
- They must be free of any unacceptable microbiologic load.
- They should not have any deleterious effect on the bioavailability of the drug in the product.
- If the drug product is also classified as food, the diluents and other excipients must be approved direct food additives.

1.9.2 Binders and Adhesives:

These materials are added either dry or in a liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets. Acacia and tragacanth are natural gums and are employed in

solutions ranging from 10-25% concentration, above or in combination. These materials are much more effective when they are added as solutions in the preparation of granulations than when they are added dry to a direct compression formula. When these materials are used, their wet granulation masses should be quickly dried at a temperature above 37^0c to reduce microbial proliferation.

1.9.3 Disintegrants[13, 14]:

A disintegrant is added to most tablet formulations to facilitate a break up or disintegrants may function by drawing water into the tablet, swelling and causing the tablet to burst apart;. Such tablet fragmentation may be critical to the subsequent dissolution of the drugs and to the attainment of satisfactory drug bioavailability. Starch USP and various starch derivatives are the most common disintegrating agents. They also have the lowest cost. Starch is typically used in a concentration range of 5 to 20% of tablet weight Such modified starches as primogel and explotab, which are low substituted carboxy methyl starches are used in lower concentration(1 to 85, with 4% usually reported as optimum). Various pregelatinized starches are also employed as disintegrants, usually in a 5% concentration.

1.9.4 Superdisintegrants[14, 15]:

When the tablet is taken orally they must dissolve easily so generally disintegrating agents are added. Moisture penetration and dispersion of the tablet matrix are there major features. In the near years several newer agents have been developed known as Super-disintegrants. These super disintegrants are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. When these come in contact with water they swell, hydrate, change volume or form and produce a disruptive change in the tablet. Good superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Disintegrants widely used in tablet manufacturing include:

Modified starches

Sodium starch glycolate is the sodium salt of a carboxy methyl ether of starch. Its concentration is effective at the range of 2-8%. High disintegration of the tablets is attained by them since they absorb 20 times its weight by which the

swelling capacity is made high. They are available in various grades i.e. Type A, B and C, which differ in pH, viscosity and sodium content. Other special grades are available which are prepared with different solvents and thus the product has a low moisture (<2%) and solvent content (<1%), thereby being useful for improving the stability of certain drugs.

Modified celluloses Carboxy methylcellulose and its derivative (Croscarmellose Sodium)

Cross-linked sodium carboxy methylcellulose is a white, free flowing powder with high absorption capacity. They have a high absorbing capacity and so they provide rapid disintegration and drug dissolution at lower levels. They have great water wicking capability and its cross-linked chemical structure creates an insoluble hydrophilic, highly absorbent material resulting ineffective swelling properties. Its recommended concentration is 0.5 to 2.0%, which can be used up to 5.0%. L-HPC (Low substituted hydroxy propyl cellulose) they are insoluble in water, swells rapidly and is used in the range of 1-5%. The grades LH- 11 and LH-21 exhibit the highest degree of swelling.

Cross-linked polyvinyl pyrrolidone

They are polymers that are insoluble. As in water they swell like others but they do not mix even after a long period of time. There rate of swelling is highest among all the superdisintegrants and is effective at 1-3%. There action is determined by wicking, swelling and possibly some deformation recovery. These polymers have a small particle size distribution that imparts a smooth mouth feel to dissolve quickly. Various grades are available commercially according to their particle size in order to achieve a uniform spreading for direct compression with the preparation.

TABLE 2: Mechanism and Concentration of Various Disintegrants

Disintegrants	Mechanism	Concentration (%)
Starch	These disintegrate, forms pathway throughout the tablet matrix. This enables the structure to draw water by capillary action leading to disruption of tablet	5-20%
Sodium starch glycolate	This involves absorption of water rapidly, which leads to drastic increase in volume of granules which result in uniform and rapid disintegration.	1-3
Pregelatinised starch	This is responsible for enhanced dissolution rate. Its rapid disintegration is due to superior swelling property.	5-15
Micro crystalline cellulose	They swell on contact with water resulting in rapid disintegration.	10-20
Crospovidone	This has capillary activity for water resulting in disintegration property of tablet.	1-3

1.9.5 Lubricants, Anti-adherents and Glidants[16]:

These three classes of materials are typically described together because they have overlapping functions. A material that is primarily described as an anti-adherent is typically also a lubricant, with some glidant properties as well.

Lubricants are intended to reduce the friction during tablet ejection between the walls of the die cavity in which the tablet was formed. Anti-adherents have the purpose of reducing sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall. Glidants are intended to promote flow of the tablet granulation or powder materials by reducing friction between the particles.

1.9.6 Colors, flavors and sweeteners:

The use of colors and dyes in tablet making has served three purposes over the years: disguising of off-color drugs, product identification, and production of a more elegant product.

The availability of natural vegetable colors is limited and these colors are often unstable. Two forms of color have typically been used in tablet preparation. These are the FD&C and D&C dyes- which are applied as solutions, typically in the granulating agent- and the lake forms of these dyes. Lakes are dyes that have been absorbed on a hydrous oxide and usually are employed as dry powders for coloring.

Flavors are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. In general, flavors that are water-soluble have found little acceptance in tablet making because of their poor stability. Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other absorbents, or are emulsified in aqueous granulating agents. Various dry flavors for use in pharmaceutical products are also available from flavor suppliers.

The use of sweeteners is primarily limited to chewable tablet to exclude or limit the use of sugar in the tablets. Mannitol is reportedly about 72% as sweet as sucrose. Saccharin was the only artificial sweetener available. This material is about 500 times sweeter than sucrose. Its major disadvantages are that it has a bitter aftertaste and has reported to be carcinogenic.

Table 3: Common Tablet Excipients:

DILUENTS	
Lactose USP Lactose USP, spray dried Lactose USP, anhydrous Micro crystalline cellulose Other cellulose derivatives	Hydrolyzed starches Dextrose Sorbitol Sucrose USP powder Sucrose based material
BINDERS AND ADHESIVES	
Acacia Cellulose derivatives Gelatin Starch, paste	Starch, pregelatinised sorbitol sodium alginate Tragacanth
DISINTEGRANTS	
Starch Cellulose Starch derivatives	Alginates PVP cross linked clays
LUBRICANTS	
Stearic acid Stearic acid derivatives Stearic acid salts Talc	Polyethylene glycols surfactants waxes
GLIDANTS AND FLOW PROMOTERS	
Silica derivatives Corn starch	Corn starch
COLOURS, FLAVOURS AND DERIVATIVES	
FD&C and D&C dyes and lakes, Spray-dried and other flavors,.	Natural sweeteners Artificial sweeteners

1.10 Hypertension[17]:

Hypertension, high blood pressure, arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is increased which requires the heart to work harder than normal. This is to circulate blood through the blood vessels. Blood pressure is measured by systolic and diastolic pressure, systolic is measured when the heart muscle is contracting and diastolic is measured when the heart muscle is relaxed between beats.

At Normal blood pressure, systolic range is 100-140mmHg (top reading) and diastolic is 60-90mmHg diastolic (bottom reading). Blood pressure is said to be high if it is persistently at or above 140/90 mmHg.

Hypertension is classified as either primary hypertension or secondary hypertension. Primary hypertension means high blood pressure with no obvious underlying medical cause where as secondary hypertension is caused by conditions that affect the kidneys, arteries, heart or endocrine system.

Hypertension is a major risk factor for stroke, myocardial infarction, heart failure, aneurysms, peripheral arterial disease. It also causes chronic kidney disease. Even moderate increase in arterial blood pressure shortens life expectancy.

Changes in Diet and lifestyle improve blood pressure control and decrease the risk of health complications. Drug treatment is necessary in people for whom above changes prove insufficient.

Table 4: Classification of anti-hypertensives[18]:

• **Diuretics**	
1. Thiazides: 2.High ceiling: 3.K^+ sparing:	Hydrochlorothiazide Chlorthalidone Furosemide. Spironolactone
• **ACE Inhibitors**	Captopril Enalapril
• **Angiotensin** **(AT_1 receptor) blockers**	Losartan Amlodipine
• **β Adrenergic blockers**	propranolol metroprolol
• **β + α adrenergic blockers**	Labetalol Carvedilol
• **α Adrenergic blockers**	Prazosin Terazosin Dexazosin
• **Central sympatholytics**	Phentolamine Clonidine Methyldopa
• **Vasodilators** 1. Arteriolar: 2. Arteriolar+venous:	Hydralazine, Minoxidil, Sodium nitropursside

1.10.1 Diuretics

Diuretics have been the standard anti-hypertensive drugs though they do not reduce BP in normotensives.

The proposed mechanism of anti-hypertensive action is

1. Initially, the diuresis reduces plasma and e.c.f volume by 5-15% decreased c.o.
2. Subsequently, compensatory mechanisms operate to almost regain Na balance and plasma volume; c.o is restored, but the fall in BP is maintained by slowly developing reduction in t.p.r.
3. The reduction in t.p.r. is mostly probably an indirect consequence of a small (~5%) persisting Na and volume deficit.

1.10.2 Calcium channel blockers[19]:

Calcium channel blockers work by blocking voltage-gated calcium channels (VGCCs) in cardiac muscle and blood vessels. This decreases intracellular calcium leading to a reduction in muscle contraction. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle and therefore an increase in arterial diameter (CCBs do not work on venous smooth muscle), a phenomenon called vasodilation. Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is determined by cardiac output and peripheral resistance, blood pressure drops. Calcium channel blockers are especially effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure in elderly patients.

1.10.3 Angiotensin II receptor blockers[20]:

These substances are AT_1-receptor antagonists – that is, they block the activation of angiotensin II AT_1 receptors. Blockage of AT_1 receptors directly causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone, amongst other actions. The combined effect reduces blood pressure.

The specific efficacy of each ARB within this class depends upon a combination of three pharmacodynamic and pharmacokinetic parameters.

Angiotensin II receptor blockers are primarily used for the treatment of hypertension where the patient is intolerant of ACE inhibitor therapy. They do not inhibit the breakdown of bradykinin or other kinins, and are thus only rarely associated with the persistent dry cough and/or angioedema that limit ACE inhibitor therapy.

1.11 Combination therapy and Fixed dose combinations[21]:

Hypertension is a major risk factor for cardiovascular, renal and stroke complications. Single-drug therapy remains the preferred way to begin treatment of hypertension. The recommendation for first-line therapy for hypertension remains a beta blocker or diuretic given in a low dosage,

A target blood pressure of less than 140/90 mm Hg is achieved in about 50 percent of patients, although in many patients this is unable to bring blood pressure (BP) to goal levels. It is increasingly appreciated that the elusive goal of a 'normal' BP is achieved only if multi-drug therapy is employed. Two or more agents from different pharmacologic classes are often needed to achieve adequate blood pressure control.

The options for multi-drug therapy are quite simple: either fixed-dose combination therapy or drugs added sequentially one after another to then arrive at an effective multi-drug regimen.

Single-dose combination anti hypertension therapy is an important option that combines efficacy of blood pressure reduction and a low side effect profile with convenient once-daily dosing to enhance compliance.

Combination antihypertensive include combined agents from the following pharmacologic classes: diuretics and potassium-sparing diuretics, beta blockers and diuretics, angiotensin-converting enzyme (ACE) inhibitors and diuretics, angiotensin-II antagonists and diuretics, and calcium channel blockers and ACE inhibitors.

Fixed-dose combination therapy successfully reduces BP because two or more drugs, each typically working at a separate site, block different effector

pathways. In addition, the second drug of such two-drug combinations may check counter-regulatory system activity triggered by the other. The pattern of adverse effects also differs with fixed-dose combination therapy, in part, because fewer drugs are generally being given. In addition, one component of a fixed-dose combination therapy can effectively counterbalance the tendency of the other to produce adverse effects.

1.12 Rationale for fixed drug combinations [21, 22]:

The rationale for using fixed-dose combination therapy is to obtain increased blood pressure control by employing two or more antihypertensive agents with different modes of action and to enhance compliance by using a single tablet that is taken once or twice daily.

Using low doses of two different agents can also minimize the clinical and metabolic effects that occur with maximal dosages of the individual components of the combined tablet.

These potential advantages are such that some investigators have recommended using combination antihypertensive therapy as initial treatment, particularly in patients with target-organ damage or more severe initial levels of hypertension.

For patients requiring 3 drugs, the combination of agents with complementary mechanisms of action (i.e., renin-angiotensin- aldosterone system blocker, calcium channel blocker, and diuretic) has been recognized as rational and effective.

Three single-pill triple-drug combinations have recently been approved for use in HTN in the United States: valsartan (VAL)/amlodipine (AML) / hydrochlorothiazide (HCTZ); olmesartan medoxomil (OM)/AML/HCTZ; and aliskiren (ALI)/VAL/HCTZ. Triple-combination regimens have resulted in a greater proportion of patients achieving BP control compared with dual combination regimens, with significantly lower BP levels

LITERATURE REVIEW

2.0 Literature review

- Steven G. Chrysant *et al*[23] has performed prespecified subgroup analysis from the triple therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in hypertensive patients. Study assessed the efficacy and safety of triple-combination treatment (olmesartan medoxomil /amlodipine besylate /hydrochlorothiazide) versus the component dual-combination treatments according to diabetes status (diabetes; non-diabetes). In participants with hypertension and diabetes, triple-combination treatment led to greater BP reductions and enabled greater proportions of participants to reach BP goal versus the dual-combination treatments. Triple-combination treatment was well tolerated in both diabetes and non-diabetes subgroups.

- Suzanne oparil *et al*[24] study was to determine whether a triple combination of olmesartan medoxomil (OM), amlodipine besylate (AML), and hydrochlorothiazide (HCTZ) had a clinically significant benefit compared with dual combinations of the individual components in patients with moderate to severe hypertension. In these adult patients with moderate to severe hypertension, triple combination was associated with significant BP reductions compared with dual combinations of the individual components. All treatments were generally well tolerated.

- Gurudutt nayak *et al*[25] compared the efficacy of triple combination (olmesartan 20 mg + amlodipine 5 mg + hydrochlorothiazide 12.5 mg) vs. dual combination (olmesartan 20 mg + amlodipine 5 mg) in patients with hypertension and proved that triple drug combination is more efficacious than dual drug combination in the treatment of patients with moderate to severe hypertension.

- Tsung-Hsien Lin *et al*[26] evaluated the efficacy and safety between a fixed dose Combinations(FDC) and a double dose(DA) for treating mild to moderate hypertension after monotherapy failure. They compared the systolic blood pressure (SBP)-lowering efficacy of the OA and DA using both an office BP and an ambulatory blood pressure monitoring (ABPM) device. This study showed that an FDC is more effective than DA in reducing SBP for mild to moderate hypertension after the failure of monotherapy.

- Giuseppe derosa *et al*[27] purpose of the study was to evaluate a fixed olmesartan/amlodipine combination on blood pressure control. The olmesartan/amlodipine combination provided a greater decrease of systolic (SBP) and diastolic blood pressures (DBP) compared with amlodipine and olmesartan monotherapies.

- Aleksandra dukic-ott *et al*[28] main aim of the study was to evaluate modified starch as the main excipient for immediate-release pellets containing poorly soluble drugs (hydrochlorothiazide and piroxicam). The bioavailability of hydrochlorothiazide pellets was not significantly different from fast disintegrating immediate-release hydrochlorothiazide tablets.

- Annke frick *et al*[29] described the development of in vitro dissolution tests using the paddle and basket apparatus with respect to the qualification/validation of the testing procedure. Three immediate release products providing different solubility characteristics are evaluated. Typically, for immediate release formulations, one limit is specified for the dissolution to ensure the release of the active ingredient within the present time period.

- C. Ferrero *et al*[30] studied the efficiency of croscarmellose sodium in direct compression formulation containing a poorly water soluble drug at a high

dose. In their study, they designed an experiment with two variables. They are applied pressure and concentration. Tablet properties were evaluated with respect to both variables while compression properties evaluated with applied pressure. Disintegration response in tablets formulated with a disintegrant which is mainly acting by swelling mechanism was optimized.

- Karrar A. Khan[31] investigated the effect of variation in compaction force on six direct compression tablet matrixes. An instrumented tablet press allowed direct measurement of applied and ejection forces. Hardness, apparent tablet density, and disintegration times also were determined. The properties studied showed varying types of dependence on compaction pressure. A direct compression formula was developed and exhibits a decrease in disintegration time as compaction force is increased.

- Y.X.Bi, H.Sunada *et al*[32] objective is to make rapidly disintegrating tablets with sufficient mechanical integrity as well as a pleasant taste. Tablets were made by a direct compression method and properties such as porosity, tensile strength, and disintegration time were determined. The tensile strength and disintegration time were selected as response variables, tablet porosity and parameters representing the characteristics of formulation were selected as controlling factors, and their relation was determined. Rapidly disintegrating tablets with durable structure and desirable taste could be prepared within the obtained optimum region.

- G. K. Bolhuis[33] formulated two drugs which are used in a low and a medium dosage range, respectively with directly compressible excipients and compressed into tablets. The results show that with a knowledge of properties and interactions of drugs, directly compressible excipients and other tablet vehicles, formulations can be composed from which tablets with good properties can be prepared.

- Tiago martinello *et al*[34] purpose of this study was to apply experimental design methodology to the development and optimization of tablet formulations and manufactured by direct compression. These results were used to generate plots for optimization, mainly for friability. The physical–chemical data found from the optimized formulation were very close to those from the regression analysis, demonstrating that the mixture project is a great tool for the research and development of new formulations.

- Markus Wirges *et al*[35] present study demonstrated that Raman spectroscopy can be successfully implemented as a process analytical technology tool to control and monitor an active-coating process of tablets. Incorporation of an active pharmaceutical ingredient (API) into the coating layer of film-coated tablets is a method mainly used to formulate combination tablets. In the present work, active-coating experiments for osmotic-controlled-release oral delivery system (OROS) tablets were performed in a side-vented lab-scale pan coater.

- Gilbert S. Banker[36] discussed the recent theory and developments relating to the formation and modification of synthetic polymeric films in relation to the pharmaceutical uses of such films in dosage form development. Fundamental mechanical and physicochemical properties of films as affected by plasticization, solvent effects, polymer chemistry, film additives, and other factors are considered in relation to film dissolution, permeability, and diffusion properties.

- Abu S. Alam[†]*et al*[37] developed two formulations using polyvinyl pyrrolidone for the film coating of tablets by the pan-coating method. The addition of ethyl cellulose and shellac eliminated the tackiness sometimes associated with polyvinyl pyrrolidone coating due to the hygroscopicity of the film former. The film coats increased the resistance of the tablet to mechanical stress, did not significantly increase the weight of the tablet, and

were physically acceptable after storage at 2° and 45°. The film coats did not interfere with the disintegration and dissolution of the tablet since the film coats were rapidly removed from the tablet in water, simulated gastric fluid, and simulated intestinal fluid.

- Raymond M. Fung† *et al*[38] used a modified balance to measure the adhesive force between the film coating and the tablet surface of 10 commercial film coated tablets. The adhesiveness or force required to remove the film coating from a unit area of tablet surface ranged from 1.06 to $4.67 \times 10^4 Nm^{-2}$. The method also was useful in studying the influence of solvents and humidity on bonding of the film coating to the tablet.

- Louise Ho *et al*[39] demonstrated that terahertz pulsed imaging (TPI) in conjunction with partial least squares regression (PLS) analysis could be employed to assist with film coating process understanding and provide predictions on drug dissolution. Understanding the coating unit operation is imperative to improve product quality and reduce output risks for coated solid dosage forms.

- Enosh M wesigwa *et al*[40] studied moisture sorption and permeability characteristics of polymer films and their effectiveness to protect a hydrolysable drug is assessed. Cast films were prepared, which were also applied onto tablet cores formulated with aspirin as a model moisture sensitive active ingredient. There was no correlation between sorption/permeability characteristics of films and their functionality as protective coatings. These results suggest that polymer coatings are not sufficiently robust to withstand moisture and do not prevent moisture-related deterioration of drugs.

- Leon Lachman *et al*[41] described the design and operation of a programmed automated tablet coating process. The electronics of the programmer, the

baffle design for the coating pan, and the spray equipment used are illustrated and discussed. The advantages and superiority of this process as compared with the customary manual coating techniques are presented.

- C. Venkata Ram *et al*[42] assessed the safety and efficacy of an amlodipine/olmesartan medoxomil (OM)-based titration regimen in patients with type 2 diabetes mellitus and hypertension. Drug-related treatment-emergent adverse events occurred in 19.3% of patients. The most frequent events were peripheral edema, dizziness and hypotension. This amlodipine/OM-based titration regimen was well tolerated and effectively lowered BP throughout the 24-hour dosing interval in patients with hypertension and type 2 diabetes.

- Julie A. Brousil *et al*[43] review describes the mechanism of action, pharmacokinetics, adverse-effect profile, drug-interaction potential, and dosing of olmesartan medoxomil. The results of relevant clinical efficacy and safety trials are also discussed. Olmesartan medoxomil has been reported to be an effective agent for the treatment of hypertension. The occurrence of clinically significant drug interactions was minimal. Olmesartan medoxomil is an effective angiotensin II-receptor blocker (ARB) for the treatment of hypertension, with a favorable adverse-effect and drug-interaction profile.

- Steven G Chrysant *et al*[44] purpose of this study was to assess the efficacy and safety of the angiotensin II receptor blocker olmesartan

medoxomil in combination with hydrochlorothiazide (HCTZ). Olmesartan medoxomil plus HCTZ produced greater reductions in both SeDBP and seated systolic blood pressure (SeSBP). Olmesartan medoxomil/HCTZ combination therapy produced BP reductions of up to 26.8/21.9 mm Hg and was well tolerated.

- Suzanne Oparil *et al*[45]performed a secondary analysis of BP efficacy data from a published study that directly compared recommended starting doses of four currently marketed ARB to assess combined SBP and DBP goal attainment. This analysis showed that the percentage of patients achieving the combined SBP/DBP goal rate of <140/90 mm Hg was highest with olmesartan medoxomil (32.4%) compared with recommended starting doses of other angiotensin II receptor blockers. Optimal ARB monotherapy can achieve recommended BP goals in a significant proportion of hypertensive patients. However, the majority of hypertensive patients will require combination therapy with two or more antihypertensive agents.

- Roberto Fogari[46] purpose of the article was to briefly review the evidence regarding the efficacy, tolerability, and potential clinical benefits of two drugs as single agents and in combination in hypertensive patients with type 2 DM. The combination has renoprotective benefits, reducing micro albuminuria and stabilizing serum creatinine levels. There is evidence that the combination increases insulin sensitivity, improves coagulation (via an increase in tissue plasminogen activity), and reduces left ventricular mass in diabetic hypertensive patients.

- Ju-Young Kim *et al*[47] aim of the study was to formulate new fixed-dose combination tablets (FCTs) by coating an immediate-release (IR) layer on a extended-release (ER) core tablet using film coating equipment. The new

FCTs were comprised of the following 3 layers: (a) an ER core tablet, (b) an inert mid-layer and (c) an outer IR layer. It was concluded that the inert mid-layer was necessary to prevent contact between ER core tablet and IR layer which retarded the release rate of IR layer. A homogeneous aqueous coating suspension was successfully prepared. The coating suspension did not contain organic solvent and thus was considered eco-friendly. the active film coating method simply required a tableting and coating machine, making it more productive and less costly.

- Alan H. Gradman[48] addressed the scientific basis of combination therapy, presented the pharmacologic rationale for choosing specific drug combinations, and review patient selection criteria for initial and secondary use. The advantages and disadvantages of single pill (fixed) drug combinations, and the implications of recent clinical trials involving specific combination strategies were also discussed.

- Mahajan HS *et al*[49] prepared rapidly disintegrating oral tablets by conventional direct compression method using different superdisintegrants like sodium starch glycolate and croscarmellose and diluents used include low substituted propyl cellulose and microcrystalline cellulose. Results showed that tablet exhibited rapid disintegration in mouth which is the characteristic feature desired**.**

- Marc S Gordan *et al*[50] investigated the effect of aging at various storage conditions on the dissolution efficiency of tablets containing three superdisintegrants which include croscarmellose, sodium starch glycolate and crospovidone using tablets prepared by wet granulation method. The super disintegrants were incorporated via three methods: extra granularly, intragranularly, or distributed equally between the two phases. The results indicated that aging decreased the dissolution efficiency of super disintegrants in wet granulated tablets. Croscarmellose sodium was affected

to a greater extent after storage than crospovidone or sodium starch glycolate. Monitoring tablet dimensions showed that there was no substantial swelling in tablets after aging at elevated humidity and temperature, except for a slight increase in thickness for tablets that contained crospovidone.

- Consuelo Souto *et al*[51]study evaluated the utility of including superdisintegrants (croscarmellose sodium or sodium starch glycolate) in microcrystalline cellulose extrusion–spheronization pellets as a means of increasing the dissolution rate of poorly water-soluble drugs. The model drug was hydrochlorothiazide, with water or water/ethanol as wetting agent for pellet preparation. Neither disintegrant caused disintegration of the pellet in drug dissolution medium. Drug dissolution rate was slightly higher in pellets prepared with sodium starch glycolate; probably because of this disintegrants higher swelling capacity.

- Mira Jivraj *et al*[52]outlined the various excipients that have been used as fillers in direct compression formulations, with particular emphasis on what is expected from such excipients in terms of their functionality. It is intended that this overview (which is by no means exhaustive) will serve as an 'aide-memoire' to the formulation scientist.

- Lucy S.C. Wan[53] studied about influence of disintegrants on disintegration time and water uptake. Disintegrants such as sodium starch glycolate (NaStglycolate), crospovidone (PVPP) and silicon dioxide (SiO_2) play an active part in influencing water uptake and disintegration time (*DT*) of sulphanilamide tablets containing methylcellulose (MC) of varying viscosity grade as a binder. The DT of tablets containing NaStglycolate decreased with an increase in the viscosity of MC due to enhanced water uptake. Tablets without MC but only the drug and NaStglycolate were observed to have a higher DT and lower water uptake at higher concentrations of the

disintegrant. The choice of excipients, especially binders such as methylcellulose, plays a crucial role in influencing disintegrant action.

- Larry augsburger L *et al*[54] outlined about the characterization and functions of superdisintegrants, the newer one's which have been developed in the recent years. They have been organized into three categories based on their chemical structure (such as sodium starch glycolate, crospovidone and croscarmellose sodium). It was concluded that adverse effects on fluidity or compactibility would be minimized and at levels lower than starch.
- H V Van Kamp *et al*[55] worked on the improvement of tablet properties by superdisintegrants. The crushing strength, disintegration and dissolution of tablet was improved when the potato starch in the formulation containing lactose as filler and gelatin as binder, is replaced by much lower concentration of an insoluble super disintegrant such as sodium starch glycolate or crospovidone. In contrast to potato starch, the position of the super disintegrants had hardly any effect on the tablet properties. The improved properties of the tablets containing insoluble super disintegrants, when compared to tablets with potato starch, are the result of the use of a much lower concentration of disintegrant.

AIM AND PLAN OF WORK

3.0 AIM AND OBJECTIVE

The aim of the present study is to formulate and evaluate a viable triple drug fixed dose combination of olmesartan medoximil, amlodipine besylate and hydrochlorthiazide film coated tablet for the treatment of hypertension.

The objective of the study:

Hypertension is a major risk factor for cardiovascular, renal and stroke complications. Since hypertension is a multi factorial condition, its control will require the administration of multiple drugs with complimentary mechanisms of action. It is, therefore, important to combine different drugs with complimentary mechanisms of action into a single pill. Recent studies have shown that triple-drug combinations are very effective, safe and well tolerated by the patients.

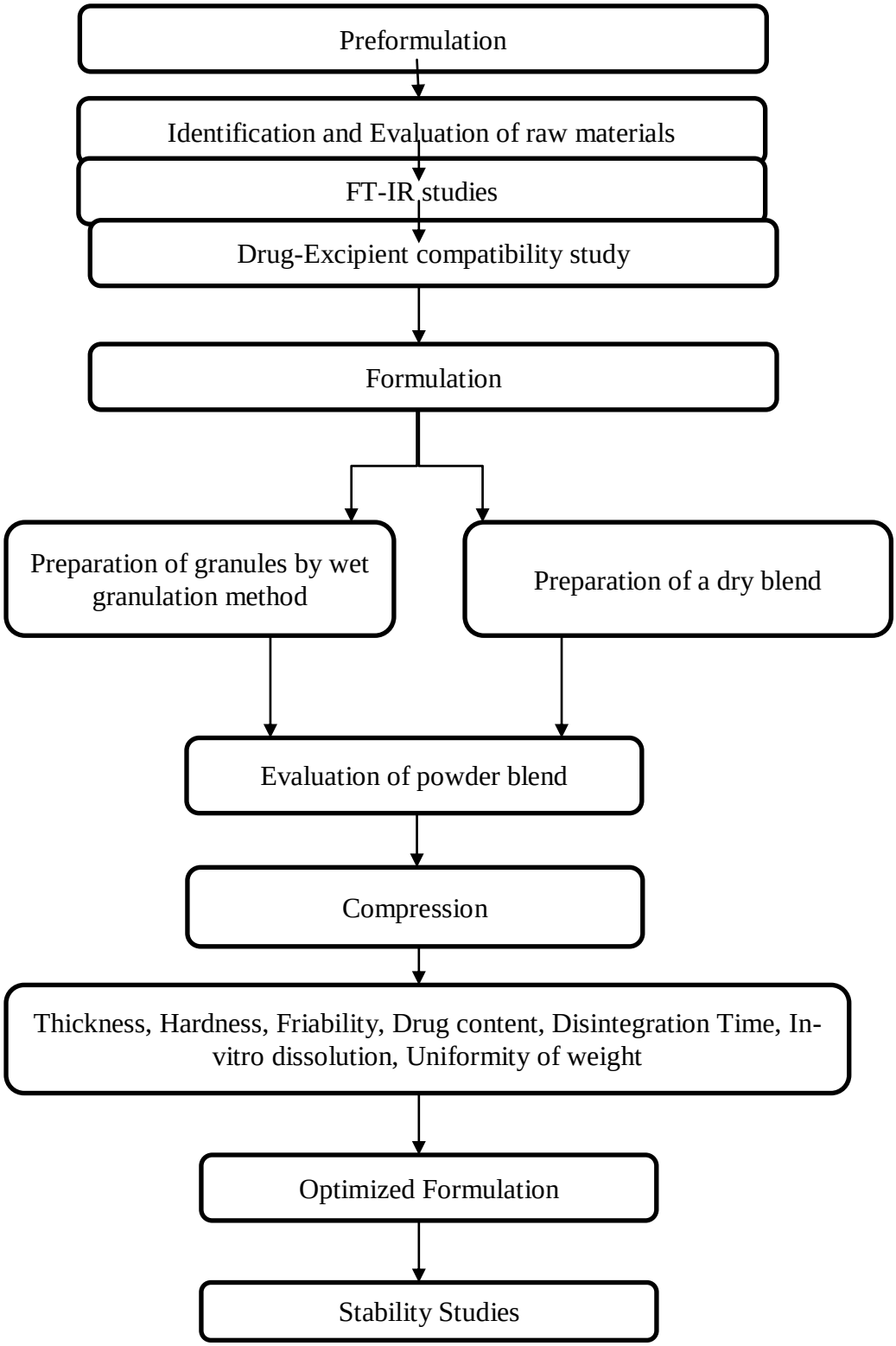
The options for multi-drug therapy are quite simple: either fixed-dose combination therapy or drugs added sequentially one after another to then arrive at an effective multi-drug regimen.

The most common combination products comprise a thiazide diuretic and a β-blocker, thus utilizing the two or more drug classes with the established outcome benefits in the treatment of hypertension. The mechanism of action of diuretics is retention of sodium by the hypertensive kidney when blood pressure is lowered by non-diuretic drugs, thus reducing antihypertensive efficacy. Thiazides minimize the sodium retention and so restore efficacy when used in combination. β-blockers lower blood pressure by decreasing cardiac output, alter baroceptor reflex sensitivity and block peripheral adrenoceptors.

Fixed dose of the above three drugs is an effective convenient and well tolerated option for treatment of patients with hypertension who require multiple anti-hypertensive drugs to achieve blood pressure control.

The objective of the present study is to develop a stable triple drug combination of olmesartan medoximil, amlodipine besylate and hydrochlorthiazide for effective and convenient use for treatment of hypertension for patients who require multiple anti-hypertensive dosing.

4.0 Plan of work



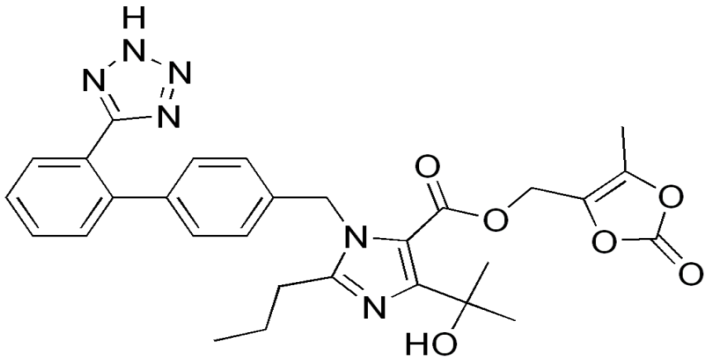
DRUG PROFILE

5.0 DRUG PROFILE:

5.1 OLMESARTAN MEDOXIMIL[55, 56] :

Trade name : Benicar, Olmetec, WinBP, Erastapex

Chemical structure:



IUPAC Name : (5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl)methyl4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2*H*-1,2,3,4 tetrazol-5-yl)phenyl]phenyl}methyl)-1*H*-imidazole-5- carboxylate

Molecular formula : $C_{29}H_{30}N_6O_6$

Molecular weight : 558.585

Melting point : 175-180^{0}C

Solubility : Insoluble in water. Sparingly soluble in strong Acid, soluble in strong base, (pH 3 to 9).

Indications : Olmesartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Dose : 20mg once daily

Loss on drying : 0.5% max

Mechanism of action:

Olmesartan is a prodrug that works by blocking the binding of angiotensin II to the AT_1 receptors in vascular muscle; it is therefore independent of angiotensin II synthesis pathways, unlike ACE inhibitors. By blocking the binding rather than the synthesis of angiotensin II, olmesartan inhibits the negative regulatory feedback

on renin secretion. As a result of this blockage, olmesartan reduces vasoconstriction and the secretion of aldosterone. This lowers blood pressure by producing vasodilation, and decreasing peripheral resistance.

Interactions:

Olmesartan may interact with nonprescription products that contain stimulants, including diet pills and cold medicines, and potassium supplements, including salt substitutes

Pharmacodynamics:

Olmesartan medoxomil is an ester prodrug for olmesartan. It is hydrolyzed to olmesartan during absorption from the GI tract. Olmesartan is a selective and competitive angiotensin II Type 1 (AT1) receptor antagonist and hence it blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II.

Pharmacokinetics:

Absorption:

Orally administered olmesartan medoxomil was rapidly absorbed from the gastrointestinal tract and converted during absorption to olmesartan, the pharmacologically active metabolite that was subsequently excreted without further metabolism.

Bioavailability: About 26%.

Tmax : Reached within 1-2 hr.

Distribution and metabolism:

The medoxomil moiety was released as diacetyl that was rapidly cleared by further metabolism and excretion. Peak plasma concentrations of olmesartan occurred 1-3 h after administration, after which concentrations decreased quickly. The elimination half-life was 10-15 h. Olmesartan medoxomil was not measurable in plasma and excreta. The volume of distribution was low, consistent with limited extravascular tissue distribution

Vd : 17 L;

Protein binding: 99%.

Excretion:

Excreted as Olmesartan in faeces via the bile (50-65%) and in urine (35-50%).

Terminal elimination half-life: About 13 hr.

Olmesartan Medoxomil Adverse Reactions / Side Effects:

Dizziness, headache, abdominal pain, dyspepsia, diarrhoea, gastroenteritis, nausea, chest pain, bronchitis, cough, pharyngitis, rhinitis, arthritis, back pain, fatigue, flu-like symptoms, hypotension, peripheral oedema, haematuria, UTI, hyperkalaemia, hypertriglyceridemia, hyperuricaemia, elevated liver enzymes, facial edema, angioedema, and rhabdomyolysis, acute renal failure.

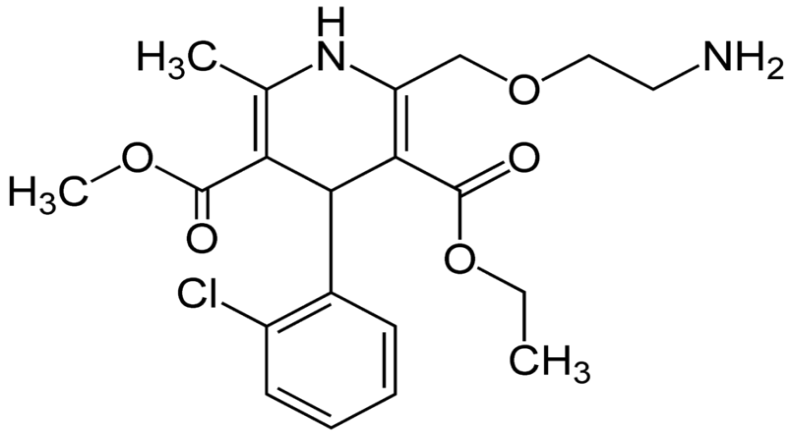
5.2 AMLODIPINE BESYLATE[57, 58]:

Category **:** Cardio vascular agent, calcium channel Blocker

Empirical Formula **:** $C_{20}H_{25}$ Cl N_2O_5

Molecular Weight **:** 408.876

Structure Formula:



Chemical Name **:** 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]

4-(2-Chlorophenyl)-1,4-dihydro-6-methyl-3,5

pyridinedicarboxylate,

Monobenzenesulphonate.

Appearance **:** A white or almost white powder.

Melting Point **:** 195 - 204 C

Solubility **:** Slightly soluble in water, freely soluble in methanol; Sparingly soluble in anhydrous

ethanol, slightly soluble in 2-orooanol.

Indications **:** Hypertension and coronary artery disease

Contraindications **:** Breast feeding, Cardiogenic shock, Unstable angina, Aortic stenosis

Interactions:

- In patients with severe coronary artery disease, amlodipine can increase the frequency and severity of angina or actually cause a heart attack on rare occasions.
- Excessive lowering of blood pressure during initiation of amlodipine treatment can occur, especially in patients already taking another medication for lowering blood pressure.

Mechanism of action:

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest amlodipine binds to both dihydropyridine and non dihydropyridine binding sites.

Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro, but such effects have not been seen in intact animals at therapeutic doses.

Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Pharmacokinetics and metabolism:

Absorption:

Amlodipine is well absorbed by the oral route with a mean oral bioavailability of approximately 60%. Results suggested that absorption of amlodipine from capsule was equivalent to that of a solution suggesting that the slow transfer of amlodipine into blood is a property of drug, not of the dosage form.

Metabolism and excretion:

Metabolism of amlodipine is complex and extensive and in common with other dihydropyridines oxidation to the pyridine analogue represents a major step. Around 5%of a dose was recovered in urine as unchanged drug. Renal elimination is the major route of excretion with about 60% of an administered dose recovered in urine, largely as inactive pyridine metabolites.

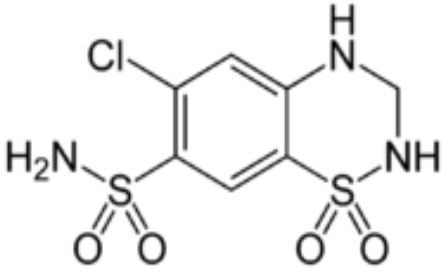
The major metabolite identified was 2-([4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl- 2-pyridyl] methoxy) acetic acid, and this represented 33% of urinary radioactivity. Amlodipine concentrations in plasma declined with a mean half-life of 33 h, while elimination of total drug-related material from plasma was slower.

5.3 Hydrochlorthiazide[59, 60]:

Molecular formula **:** $C_7H_8ClN_3O_4S_2$

Molecular weight **:** 297.7

Molecular structure **:**



Chemical Name : 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide**.**

Description : White to almost white crystalline powder

Solubility : white to almost white colored crystalline powder which is freely soluble in water, soluble in methanol, sparingly soluble in alcohol and slightly soluble in Isopropyl alcohol

Melting point : 274 ^{0}C

Therapeutic category **:** Antihypertensive Agents

Diuretics

Sodium Chloride Symporter Inhibitors

General Description:

A thiazide diuretic often considered the prototypical member of this class. It reduces the reabsorption of electrolytes from the renal tubules. This results in

increased excretion of water and electrolytes, including sodium, potassium, chloride and magnesium. It has been used in the treatment of several disorders including edema, hypertension, diabetes insipid us, and hypo parathyroidism.

Mechanism of Action:

Thiazide diuretics act in the distal convoluted tubule, where they block Na-Cl co-transport. The Na–Cl cotransport takes place on the luminal surface of distal convoluted tubules. Thus, to exert their diuretic action; the thiazides must reach the luminal fluid. Since the thiazide diuretics are largely bound to plasma proteins and therefore are not readily filtered across the glomeruli, access to the luminal fluid is accomplished by the proximal tubule organic acid secretory system.

The drugs then travel along the nephron, presumably being concentrated as fluid is abstracted, until they reach their site of inhibitory action in the distal convoluted tubule. Especially at higher doses, administration of some of the thiazides results in some degree of carbonic anhydrate inhibition. However, at usual doses, only chlorothiazide shows any appreciable carbonic anhydride inhibitory activity.

Pharmacokinetics

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

Absorption and Elimination:

Orally administered thiazides are rapidly absorbed from the gastrointestinal tract and begin to produce dieresis in about 1 hour. Approximately 50% of an oral dose is excreted in the urine within 6 hours.

These compounds are organic acids and are actively secreted into the proximal tubular fluid by the organic acid secretary mechanism. There also appears to be an extra renal pathway for their elimination involving the hepatic–biliary acid

secretary system that is particularly important for thiazide elimination when renal function is impaired.

The thiazides have a variable effect on elimination of uric acid, which also is secreted by the renal acid secretary mechanism. Administration of thiazide diuretics, especially at low doses, may elevate serum uric acid levels and cause gout like symptoms.

Following large doses, thiazides may compete with uric acid for active reabsorption and thereby may promote uric acid elimination rather than impair it.

Adverse Effects

Thiazides should be used cautiously in the presence of severe renal and hepatic disease, since azotemia and coma may result. The most important toxic effect associated with this class of diuretics is hypokalemia, which may result in muscular and central nervous system symptoms, as well as cardiac sensitization. Periodic examination of serum electrolytes for possible imbalances is strongly recommended.

Appropriate dietary and therapeutic measures for controlling hypokalemia are described later in this chapter. The thiazides also possess some diabetogenic potential, and although pancreatitis during thiazide therapy has been reported in a few cases, the major mechanism contributing to the potential for glucose intolerance is not known.

EXCIPIENT PROFILE

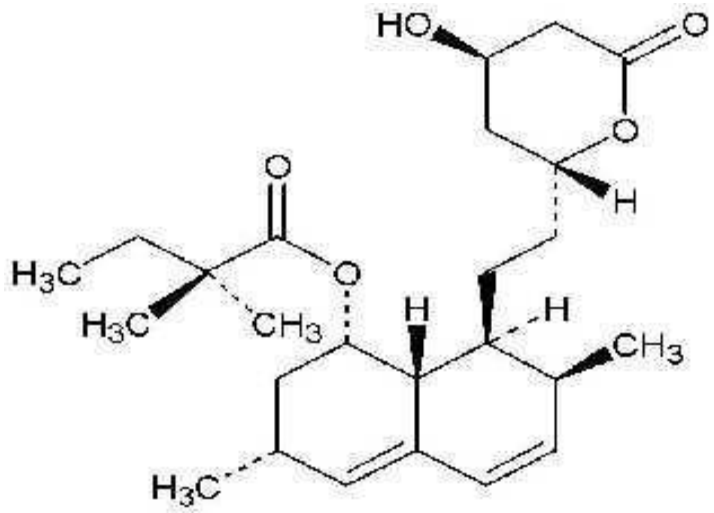
6.0 EXCIPIENT PROFILE:

6.1 Croscarmellose sodium[61]:

Non Proprietary Name **:** USPNF: Croscarmellose sodium.
JP: Croscarmellose Sodium
PhEur: Croscarmellose Sodium
USP-NF: Croscarmellose Sodium

Synonyms **:** Ac-Di-sol; cross-linked carboxy methylcellulose sodium; Primellose; Solutab; Vivasol.

Structural Formula **:**



Functional category **:** Tablet and capsule disintegrant.

Chemical name **:** Cellulose, carboxy methyl ether, sodium salt,

Description : Croscarmellose sodium occurs as an odorless, white colored powder.

Molecular weight : 90000-700000.

PH : 5.0-7.0.

Solubility : Insoluble in water. Although croscarmellose sodium rapidly swells to 4-8 times of its original volume on contact with water.

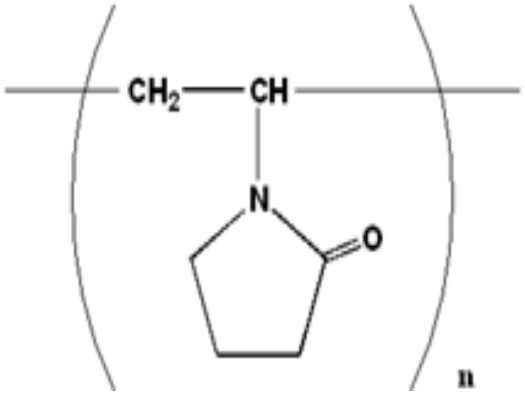
Stability, Storage Condition: Croscarmellose sodium is a stable though hygroscopic material. Croscarmellose sodium should be stored in a well-closed container in a cool place.

Incompatibilities : The efficacy of disintegrants, such as Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by wet granulation or direct compression process which contain hygroscopic material such as sorbitol.

Safety : Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material.

6.2 CROSPOVIDONE[62]:

Nonproprietary Names	**:**	Crospovidone PhEur: Crospovidone USP-NF: Crospovidone
Synonyms	**:**	Crospovidonum;Crospopharm; crosslinkedpovidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; PolyplasdoneXL-10; PVPP;
Chemical Name	**:**	1-Ethenyl-2-pyrrolidinonehomopolymer
CAS Registry Number	**:**	[9003-39-8]
Empirical Formula	**:**	(C6H9NO)n>1 000 000
Molecular Formula	**:**	A water-insoluble syntheticcrosslinked Homopolymer of N-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.
Structural Formula	**:**	



Functional Category **:** Tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

- Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.
- The particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles.
- Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.
- The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description:

Crospovidone is a white to creamy-white, finely divided, free flowing, and practically tasteless, odorless or nearly odorless, hygroscopic powder.

Stability and Storage Conditions:

Since crospovidone is hygroscopic, it should be stored in an air tight container in a cool, dry place.

Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

Method of Manufacture:

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone.

Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidoneandacetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a 'popcorn polymerization' process.

Safety:

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short term animal toxicity studies have shown no adverse effects associated with crospovidone.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA.

6.3 SODIUM STARCH GLYCOLATE63:

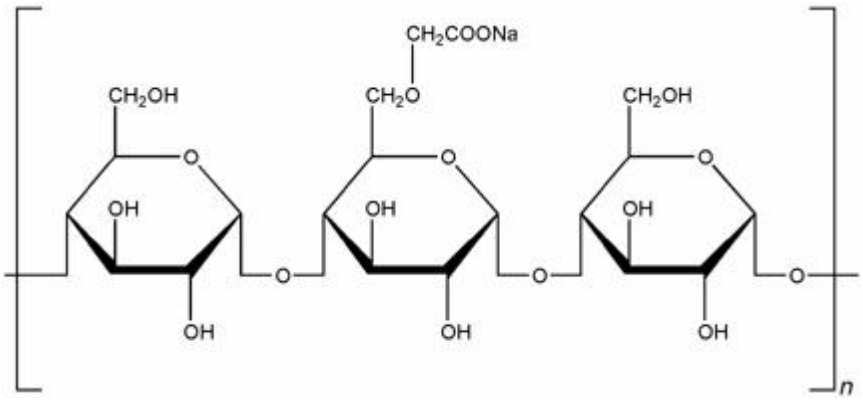
Nonproprietary Names **:** BP: Sodium Starch Glycolate
PhEur: Sodium starch Glycolate
USPNF:SodiumStarchGlycolate

Synonyms **:** Carboxymethyl starch, sodium salt; carboxymethylamylumnatricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

Chemical Name **:** Sodium carboxymethyl starch

CAS Registry Number **:** [9063-38-1]

Structural Formula **:**



Functional Category **:** Tablet and capsule disintegrant.

Weight loss on drying% : ≤ 0.003

Appearance **:** White or off white powder, odorless,

		moisture absorptive in air
Particle size	**:**	100% through 120 mesh sieve
Solubility	**:**	insoluble in ethanol, or sulfuric ether; dispersing in water or becoming viscous colloid solution.

Applications in Pharmaceutical Formulation or Technology:

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.
- It is commonly used in tablets prepared by either direct-compression or wet-granulation processes.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description:

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of: granules irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded, 10–35 mm in size; compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations.

Stability and Storage Conditions:

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

Method of Manufacture:

Sodium starch glycolate is a substituted derivative of potato starch. Typically, commercial products are also cross linked using either sodium trimetaphosphate (Types A and B) or dehydration (Type C).

Starch is carboxy methylated by reacting it with sodium chloro acetate in an alkaline, non-aqueous medium, typically denatured ethanol or methanol, followed by neutralization with citric acid, acetic acid, or some other acid.

Safety:

Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended. A dust mask or respirator is recommended for processes that generate a large quantity of dust.

Regulatory Acceptance:

Included in the FDA Inactive Ingredients Database

6.4 Colloidal Silicon Dioxide[64]

Nonproprietary Names	**:** BP: Colloidal Anhydrous Silica JP: Light Anhydrous Silicic Acid PhEur: Silica, Colloidal Anhydrous USP-NF: Colloidal Silicon Dioxide
Synonyms	**:**Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; fumed silicon dioxide; SAS; silica colloidalisanhydrica; silica sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica;
Empirical Formula	**:** SiO_2,
Molecular Weight	**:** 60.08
Structure	**:** SiO_2
Functional Category	**:**Adsorbent; anticaking agent; emulsion Stabilizer;glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

- Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products;
- Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations
- Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.
- Colloidal silicon dioxide is frequently added to suppository formulations

Description:

Colloidal silicon dioxide is submicroscopic fumed silica with particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

Incompatibilities:

Incompatible with diethylstilbestrol preparations

Method of Manufacture:

Colloidal silicon dioxide is prepared by the flame hydrolysis of chlorosilanes, such as silicon tetrachloride, at 18008C using a hydrogen–oxygen flame. Rapid cooling from the molten state during manufacture causes the product to remain amorphous.

Stability and Storage Conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying.

Colloidal silicon dioxide powder should be stored in a well-closed container.

Safety:

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

6.05 Starch, Sterilizable Maize[65] :

Nonproprietary Names **:** USP: Absorbable Dusting Powder

Synonyms **:** Bio-sorb; double-dressed, white maize starch;

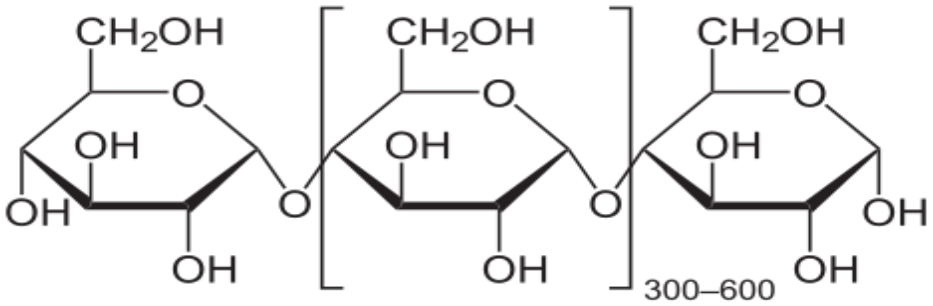
Fluid amid R444P; Keoflo ADP; Meritena; modified starch dusting powder; Pure-DentB851; starch-derivative dusting powder; sterilizable corn starch.

Chemical Name **:** Sterilizable maize starch

Empirical Formula and Molecular Weight: $(C_6H_{10}O_5)_n$

where n = 300–1000.Sterilizable maize starch is a modified corn (maize) starch that may also contain up to 2.0% of magnesium oxide.

Structural Formula



Functional Category **:** Diluent; lubricant.

Applications in Pharmaceutical Formulation or Technology

- Sterilizable maize starch is a chemically or physically modified corn (maize) starch that does not gelatinize on exposure to moisture or steam sterilization.

- Sterilizable maize starch is primarily used as a lubricant for examination and surgeons' gloves, although because of safety concerns unlubricated gloves are now generally recommended;
- It is also used as a vehicle for medicated dusting powders.

Description

Sterilizable maize starch occurs as an odorless, white, free-flowing powder. Particles may be rounded or polyhedral in shape.

Stability and Storage Conditions:

Sterilizable maize starch may be sterilized by autoclaving at 121^0C for 20 minutes, by ethylene oxide, or by irradiation.

Method of Manufacture

Corn starch (maize starch) is physically or chemically modified by treatment with either phosphorus oxychloride or epichlorhydrin so that the branched-chain and straight-chain starch polymers crosslink. Up to 2.0% of magnesium oxide may also be added to the starch.

Safety

Sterilizable maize starch is primarily used as a lubricant for surgeons' gloves and as a vehicle for topically applied dusting powders. Granulomatous reactions, peritonitis and inflammation at operation sites have been attributed to contamination with surgical glove powders containing sterilizable maize starch. In addition, glove powder may be a risk factor in the development of latex allergy. As a consequence, it has been suggested that the use of sterilizable maize starch in latex gloves should be prohibited.

Regulatory Status

Included in the FDA Inactive Ingredients Database

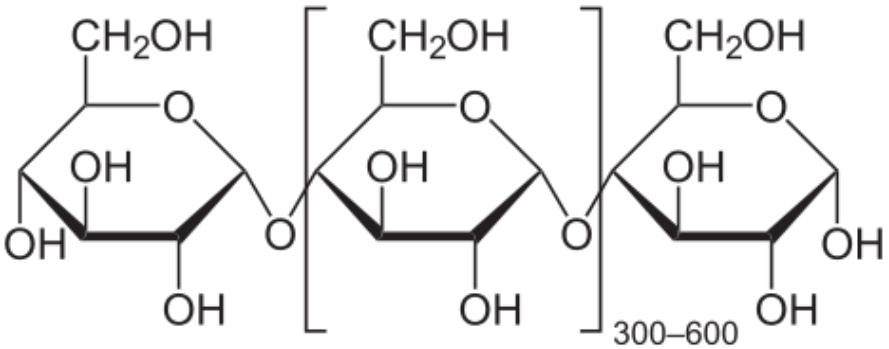
6.06 Starch, Pregelatinized[66]:

Nonproprietary Names	**:**	BP: Pregelatinised Starch PhEur: Starch, Pregelatinised USP-NF: Pregelatinized Starch
Synonyms	**:**	Amylumpregelificatum; compressible Starch C*PharmGel; Instastarch; Lycatab C;Lycatab PGS; Merigel; National 78-1551; Pharma-Gel; Prejel; Sepistab ST200; Spress B820; Starch 1500 G; Tablitz; Unipure LD; Unipure WG220.
Chemical Name	**:**	Pregelatinized starch
CAS Registry Number	**:**	[9005-25-8]

Empirical Formula and Molecular Weight: $(C_6H_{10}O_5)_n$

where n = 300–1000.

Structural Formula **:**



Functional Category	**:**	Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Applications in Pharmaceutical Formulation or Technology:

- Partially pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluents and disintegrant.
- .Both partially and fully pregelatinized starch may also be used in wet granulation processes
- Fully pregelatinized starches can be used to make soft capsules, shells, and coatings as well as binders in tablets.

Description:

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Stability and Storage Conditions:

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

Method of Manufacture:

Food-grade pregelatinized starches are prepared by heating an aqueous slurry containing up to 42% w/w of starch at 62–728C. Chemical additives that may be included in the slurry are gelatinization aids (salts or bases) and surfactants, added to control rehydration or minimize stickiness during drying. After heating, the slurry may be spray-dried, roll-dried, extruded, or drum-dried. In the last case, the dried material may be processed to produce a desired particle size range.

Safety:

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and

nonirritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion.

6.07 Cellulose, Microcrystalline[67]:

Nonproprietary Names **:** BP: Microcrystalline Cellulose
JP: Microcrystalline Cellulose
PhEur: Cellulose, Microcrystalline
USP-NF: Microcrystalline Cellulose

Synonyms **:** Avicel PH; Cellets; Celex; cellulose gel; hellulosummicrocristallinum; Celphere: Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur

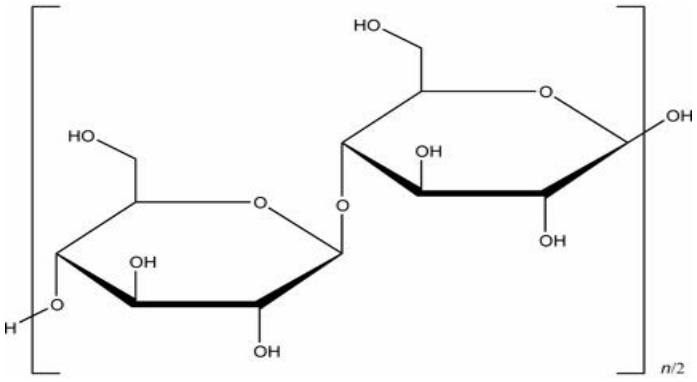
Chemical Name **:** Cellulose

CAS Registry Number **:** [9004-34-6]

Empirical Formula **:** $(C_6H_{10}O_5)n$ **,** Where n - 220.

Molecular Weight **:** ≈36 000

Structural Formula **:**



Functional Category **:** Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.

In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Description:

Microcrystalline cellulose is purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Method of Manufacture:

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of a-cellulose, obtained as a pulp from fibrous plant materials.

Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray dried to form dry, porous particles of a broad size distribution.

Safety:

Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended

Regulatory Status:

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations;.

6.08 Magnesium Stearate[68]:

Nonproprietary Names	**:**	BP: Magnesium Stearate JP: Magnesium Stearate PhEur: Magnesium Stearate USP-NF: Magnesium Stearate
Synonyms	**:**	Dibasic magnesium stearate; magnesium distearate; magnesiistearas; magnesium octadecanoate; octadecanoic acid, magnesiumsalt; stearic acid, magnesium salt; Synpro 90.
Chemical Name	**:**	Octadecanoic acid magnesium salt
CAS Registry Number	**:**	[557-04-0]
Empirical Formula	**:**	$C_{36}H_{70}MgO_4$
Molecular Weight	**:**	591.24
Structural Formula	**:**	$[CH_3(CH_2)_{16}COO]_2Mg$
Functional Category	**:**	Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Method of Manufacture:

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

Safety:

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation. No toxicity information is available relating to normal routes of occupational exposure.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended

Regulatory Acceptance:

GRAS listed. Accepted as a food additive in the USA and UK. Included in the FDA

6.09 Titanium Dioxide[69]

Nonproprietary Names	**:**	BP: Titanium Dioxide JP: Titanium Oxide PhEur: Titanium Dioxide USP: Titanium Dioxide
Synonyms	**:**	Anatase titanium dioxide; brookite titanium dioxide; color index number 77891; E171; Hombitan FF-Pharma; Kemira AFDC; Kronos 1171; pigment white 6; Pretiox AV-01-FG; rutile titanium dioxide; Tioxide; TiPure; titanic anhydride; titaniidioxidum;
Chemical Name	**:**	Dioxotitanium
CAS Registry Number	**:**	[13463-67-7]
Empirical Formula	**:**	TiO_2
Molecular Weight	**:**	79.88
Structural Formula	**:**	TiO_2
Functional Category	**:**	Coating agent; opacifier; pigment.

Applications in Pharmaceutical Formulation or Technology:

- Titanium dioxide is widely used in confectionery, cosmetics, and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment.

- Owing to its high refractive index, titanium dioxide has light scattering properties that may be exploited in its use as a white pigment and opacifier.
- In pharmaceutical formulations, titanium dioxide is used as a white pigment in film-coating suspensions, sugar-coated tablets, and gelatin capsules.
- Titanium dioxide may also be admixed with other pigments.
- Titanium dioxide is also used in dermatological preparations and cosmetics, such as sunscreens.

Description:

White, amorphous, odorless, and tasteless non hygroscopic powder. Although the average particle size of titanium dioxide powder is less than 1 mm, commercial titanium dioxide generally occurs as aggregated particles of approximately 100 mm diameter. Titanium dioxide may occur in several different crystalline forms: rutile; anatase; and brookite.

Stability and Storage Conditions:

Titanium dioxide is extremely stable at high temperatures. This is due to the strong bond between the tetravalent titanium ion and the bivalent oxygen ions. However, titanium dioxide can lose small, unweighable amounts of oxygen by interaction with radiant energy.

This oxygen can easily recombine again as a part of a reversible photo chemical reaction, particularly if there is no oxidizable material available. These small oxygen losses are important because they can cause significant changes in the optical and electrical properties of the pigment.

Titanium dioxide should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities:

Owing to a photocatalytic effect, titanium dioxide may interact with certain active substances, e.g. famotidine

Method of Manufacture:

Titanium dioxide occurs naturally as the minerals rutile (tetragonal structure), anatase (tetragonal structure), and brookite (orthorhombic structure). Titanium dioxide may be prepared commercially by either the sulfate or chloride process.

In the sulfate process, titanium containing ore, such as ilemenite, is digested in sulfuric acid. This step is followed by dissolving the sulfates in water, then precipitating the hydrous titanium dioxide using hydrolysis.

Finally, the product is calcinated at high temperature. In the chloride process, the dry ore is chlorinated at high temperature to form titanium tetrachloride, which is subsequently oxidized to form titanium dioxide.

Safety:

Titanium dioxide is widely used in foods and oral and topical pharmaceutical formulations. It is generally regarded as an essentially nonirritant and nontoxic excipient.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. Titanium dioxide is regarded as a relatively innocuous nuisance dust,(9) that may be irritant to the respiratory tract.

Regulatory Status:

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients

6.10 Talc[70]:

Nonproprietary Names	**:**	BP: Purified Talc JP: Talc PhEur: Talc USP: Talc
Synonyms	**:**	Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; MagsilOsmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.
Chemical Name	**:**	Talc
CAS Registry Number	**:**	[14807-96-6]
Empirical Formula	**:**	Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.
Functional Category	**:**	Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluents
- It is widely used as a dissolution retardant in the development of controlled-release products
- Talc is also used as a lubricant in tablet formulations
- In a novel powder coating for extended-release pellets and as an adsorbant.
- In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.
- Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.
- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.

Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds.

Method of Manufacture:

Naturally occurring talc is mined and pulverized before being subjected to flotation processes to remove various impurities such as asbestos (tremolite); carbon; dolomite; iron oxide; and various other magnesium and carbonate minerals.

Following this process, the talc is finely powdered, treated with dilute hydrochloric acid, washed with water, and then dried. The processing variables of agglomerated talc strongly influence its physical characteristics.

Safety:

Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. Intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs .

Contamination of wounds or body cavities with talc may also cause granulomas; been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis

Regulatory Status:

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database

Related Substances:

Bentonite; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate.

6.11 Polyethylene Glycol[71]:

Nonproprietary Names	**:**	BP: Macrogols JP: Macrogol 400 Macrogol 1500 Macrogol 4000 Macrogol 6000 Macrogol 20000 PhEur: Macrogols USP-NF: Polyethylene Glycol
Synonyms	**:**	Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG;Pluriol E; polyoxyethylene glycol.
Chemical Name	**:**	a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)
CAS Registry Number	**:**	[25322-68-3]
Empirical Formula	**:**	$HOCH_2(CH_2OCH_2)mCH_2OH$ where m represents the average number of oxyethylene groups.
Functional Category	**:**	Ointment base; plasticizer; solvent; Suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

- Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations.

- Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.(1)
- Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin;
- Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol. Mixtures of polyethylene glycols can be used as suppository bases.

Description:

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Stability and Storage Conditions:

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.

Method of Manufacture:

Polyethylene glycol polymers are formed by the reaction of ethylene Method of Manufacture Polyethylene glycol polymers are formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

Safety:

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported,

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

Regulatory Status:

Included in the FDA Inactive Ingredients Database (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations).

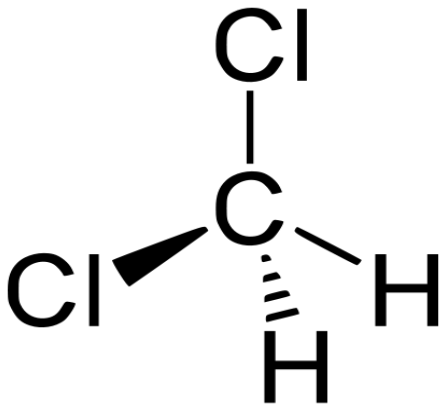
Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal
Ingredients.

Related Substances:

Polyoxyethylene alkyl ethers; polyethylene oxide; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene stearates; suppository bases.

6.12 Methylene chloride[72]:

Synonyms	**:**	Methylene chloride, methylene dichloride, Solmethine, Narkotil, Solaesthin, Di-clo, Freon 30, R-30, DCM, UN 1593, MDC
Chemical Name	**:**	Dichloromethane
Empirical Formula	**:**	CH_2CL_2
Molecular Weight	**:**	84.93g/mol
Density	**:**	1.33 g/cm³
Boiling point	**:**	39.6 °C
Melting point	**:**	-96.7 °C
IUPAC ID	**:**	Dichloromethane
Structural Formula	**:**	



Functional Category	**:**	Solvent

Applications in Pharmaceutical Formulation or Technology:

- Its volatility and ability to dissolve a wide range of organic compounds makes it a useful solvent for many chemical processes.
- It is widely used as a paint stripper and a degreaser.
- In the food industry, it has been used to decaffeinate coffee and tea as well as to prepare extracts of hops and other flavorings.
- Its volatility has led to its use as an aerosol spray propellant and as a blowing agent for polyurethane foams.

Description:

Methylene chloride is a colorless, volatile liquid with a moderately sweet aroma.

Method of Manufacture:

DCM is produced by treating either methyl chloride or methane with chlorine gas at 400–500 °C. Both methane and methyl chloride undergo a series of reactions producing more chlorinated products.

$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$

$CH_3Cl + Cl_2 \rightarrow CH_2Cl_2 + HCl$

$CH_2Cl_2 + Cl_2 \rightarrow CHCl_3 + HCl$

$CHCl_3 + Cl_2 \rightarrow CCl_4 + HCl$

The result of these processes is a mixture of methyl chloride, dichloro methane, chloroform, and carbon tetrachloride. These compounds are separated by distillation.

Toxicity:

- DCM is the least toxic chlorohydrocarbons. But because of its high volatility, can cause acute inhalation hazard.
- It is metabolized by the body to carbon monoxide potentially leading to carbon monoxide poisoning.
- Acute exposure by inhalation results in optic neuropathy and hepatitis.
- Prolonged skin contact cause DCM dissolving some of the fatty tissues in skin, resulting in skin irritation or chemical burns.

6.13 Isopropyl Alcohol[73]:

Nonproprietary Names	**:**	BP: Isopropyl Alcohol JP: Isopropanol PhEur: Isopropyl Alcohol USP: Isopropyl Alcohol
Synonyms	**:**	Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec-propyl alcohol; rubbing alcohol.
Chemical Name	**:**	Propan-2-ol
CAS Registry Number	**:**	[67-63-0]
Empirical Formula	**:**	C_3H_8O
Molecular Weight	**:**	60.1
Functional Category	**:**	Disinfectant; solvent.

Applications in Pharmaceutical Formulation or Technology:

- Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations
- Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly
- Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation,where the isopropyl alcohol is subsequently removed by evaporation.
- It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934.
- Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant.

- Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Description

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

Stability and Storage Conditions:

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

Method of Manufacture:

Isopropyl alcohol may be prepared from propylene; by the catalytic reduction of acetone, or by fermentation of certain carbohydrates.

Safety:

Isopropyl alcohol is widely used in cosmetics and topical pharmaceutical formulations. It is readily absorbed from the gastrointestinal tract and may be slowly absorbed through intact skin. Prolonged direct exposure of isopropyl alcohol to the skin may result in cardiac and neurological deficits. In neonates, isopropyl alcohol has been reported to cause chemical burns following topical application.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Isopropyl alcohol may be irritant to the skin, eyes, and mucous membranes upon inhalation. Eye protection and gloves are recommended. Isopropyl alcohol should be handled in a well-ventilated environment

Regulatory Status

Included in the FDA Inactive Ingredients Database

6.14 HPMC[74]:

Nonproprietary Names	**:**	BP: Hypromellose JP: Hydroxypropylmethylcellulose PhEur: Hypromellosum USP: Hypromellose
Synonyms	**:**	Benecel MHPC; E464; hydroxypropyl Methyl cellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.
Chemical Name	**:**	Cellulose hydroxypropyl methyl ether
CAS Registry Number	**:**	[9004-65-3]
Molecular Weight	**:**	Molecular weight is approximately 10,000 – 1,500,000.
Structural Formula	**:**	$CH_3\,CH(OH)CH_2$
Functional Category	**:**	Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet

binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
- In oral products, hypromellose is primarily used as a tablet binder in film-coating and as a matrix for use in extended-release tablet formulations.
- Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.
- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.
- Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.
- Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.
- As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- Hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description:

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder

Typical Properties:

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Ash: 1.5–3.0%, depending upon the grade and viscosity.

Auto ignition temperature: 360^0C

Density (bulk): 0.341 g/cm^3

Density (tapped): 0.557 g/cm^3

Density (true) : 1.326 g/cm^3

Melting point: browns at 190–200^0C; chars at 225–230^0C.

Glass transition temperature is 170–180^0C.

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. Aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative.

Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities:

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Method of Manufacture:

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce swollen alkali cellulose that is chemically more reactive than untreated cellulose.

The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

Safety:

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. Hypromellose is generally regarded as a nontoxic and nonirritant.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide

MATERIALS

MATERIALS

Table 6: Materials used in Manufacturing

List of Materials used in the Study	Materials Manufacturer/Suppliers
Olmesartanmedoximil	Sequel, Glenmark
Amlodipine besylate	Arch Pharma labs
Hydrochlorthiazide	CPS Pharm labs
Pregelatinised starch	RoquetteFreres,France
Maize starch	Universal starch chem
Mcc ph 102	Ran Q
Colloidal silicon dioxide	Cabot Sanmar ltd
Croscarmellose sodium	FMC Biopolymer
Sodium starch glycolate	Vasa pharmachem
crospovidone	ISP
Magnesium stearate	Amishi Drugs & Chemicals Ltd
HPMC E15	DOW
Titanium dioxide	KRONOS International
Purified Talc	Bharat Pharmaceuticals
PEG 400	Parchem
Methylene chloride	Gujarat Allealis& Chemicals
Isopropyl alcohol	Lee Changyung Chemicals

Table 7: LIST OF EQUIPMENTS

Sl. No	Materials	Manufacturers/ Suppliers
1	Moisture balance	Sartorius, Germany
2	Vibratory sifter	Bectochem
3	Planetary mixer (vertical main drive)	Bectochem
4	Hexagonal blender	Bectochem
5	Rapid mixer granulator	Bectochem
6	Fluidised bed dryer	Bectochem
7	Tray drier	Micro, S.B Panchal& co, India
8	Multimill	Bectochem
9	Double rotary Compression machine(27 station)	Cadmach, India
10	dehumidifier	Tropical nortec, India
11	Vernier caliper	Mitutoyocorp, Japan
12	Blister packing machine	Labmodule, India
13	Photo stability &humidity chamber	Thermo labs India Ltd

Table 8: List of Instruments:

Sl. No	Instruments	Manufacturers/ Suppliers
1	Electronic weighing balance	Shimadzu corporation, Japan
2	pH Meter	Mettler, Toledo, India.
3	Tap Density apparatus, ETD-1020	Electro lab, India.
4	Hardness tester	Monsanto , India
5	Friability Test Apparatus, ET-2	Electro lab, India.
6	Dissolution Apparatus, TDT-08L,	Electro lab, India.
7	Disintegration Apparatus	Electro lab, India.
8	FT-IR Spectrophotometer 8300	Shimadzu corporation, Japan
9	Differential scanning colorimetry	DSC Q2000 V24.4 build 114
10	UV- Visible Spectrophotometer (UV-1601)	Shimadzu corporation, Japan
11	HPLC with PDA detector	Waters HPLC, India.
12	Refrigerator	Whirlpool, India

Table 9: List of Reagents

Sl. No	Reagents/ chemicals	Manufacturers/suppliers
1	Potassium dihydrogen ortho phosphate AR	Rankem, New Delhi.
2	Sodium hydroxide AR	Rankem New Delhi.
3	Acetonitrile HPLC	Merck Canada.
4	Methanol HPLC	Merck, Canada.
5	Sodium dihydrogen ortho phosphate AR	Rankem, New Delhi.
6	Ortho phosphoric acid AR	Rankem, New Delhi.
7	Hydrochloric acid AR	Rankem, New Delhi
8	Whatman filter paper	Sartourious 292A, North America.
9	0.45 µ filter paper	Millipore, Canada.

METHODS

7.0 EXPERIMENTAL WORK:

7.1 PREFORMULATION [75]:

Preformulation can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. The type of information needed will depend on the dosage form to be developed. The formal preformulation study should start at the point after biological screening, when a decision is made for further development of the compound in clinical trials.

7.2 EVALUATION OF RAW MATERIALS:

7.2.1 Calibration curve:

Preparation of standard solution for calibration curve of olmesartan medoximil[76]:

10 mg Standard Olmesartan Medoxomil was accurately weighed and transferred to 100 ml volumetric flask and was dissolved properly and diluted up to the mark with methanol to produce a stock solution of 100 µg/ml. Appropriate amounts of this stock solution were diluted with the same solvent, which yield concentrations of 4µg/ml, 6µg/ml, 8µg/ml 10µg/ml, 12µg/ml and 14µg/ml and were used for the construction of calibration curve.

Preparation of standard solution for calibration curve for Amlodipine besylate:

100mg of Amlodipine besylate was accurately weighed and dissolved in 25ml of methanolin100ml volumetric flask and the volume was made upto the mark using methanol, to make (1000µg/ml) standard stock solution(I). Then 1ml stock solution(I) was taken in another 100ml volumetric flask and further dilute in 100ml of methanol to make(10µg/ml) standard stock solution(II), then final concentrations were prepared 10,20,30,40 and 50µg/ml with 0.1N HCL. The

absorbance of standard solution was determined using UV/VIS spectrophotometer at236nm

Preparation of standard solution for calibration curve of hydrochlorthiazide:

Weigh accurately 0.025gm of hydrochlorothiazide was taken in to 100ml of standard flask, and added small volume of methanol and shake well after that make up to the volume with 100 ml (stock solution), from this solution 10 ml and transferred in to 50 ml standard flask and made up to 50 ml with methanol (which is consist of 50 µg/ml used for the analysis), from the above solution, the sample solution was prepared from five different concentrations using methanol as a solvent like 10,20,30,40,and 50µg/ml were used for the calibration curve analysis

PREPARATION OF BUFFER SOLUTIONS[78]:

Preparation of 0.1N Hydrochloric Acid (1.2pH):

8.5 ml of the hydrochloric acid was taken and dissolved in water and made upto 1000 ml to get 0.1N hydrochloric acid.

Preparation of Phosphate buffer solution (6.8pH):

50 ml of 0.02 M Potassium dihydrogen phosphate was taken in a 200 ml volumetric flask. 22.4 ml of 0.02 M sodium hydroxide solution was added and the volume was made up to 200 ml using distilled water.

7.2.2 Raw material analysis for Olmesartan Medoximil [76]**:**

Raw material analysis of Olmesartan Medoximil was done as per IP. Identification test was carried out by the Fourier Transform Infra-red spectrophotometer (FTIR). The report was shown in fig: 9.

7.2.3 Raw material analysis for Amlodipine Besylate:

Raw material analysis of Amlodipine Besylate was done as per IP. Identification test was carried out by the Fourier Transform Infra-red spectrophotometer (FTIR). The report was shown in fig: 10.

7.2.4 Raw material analysis for Hydrochlorthiazide:

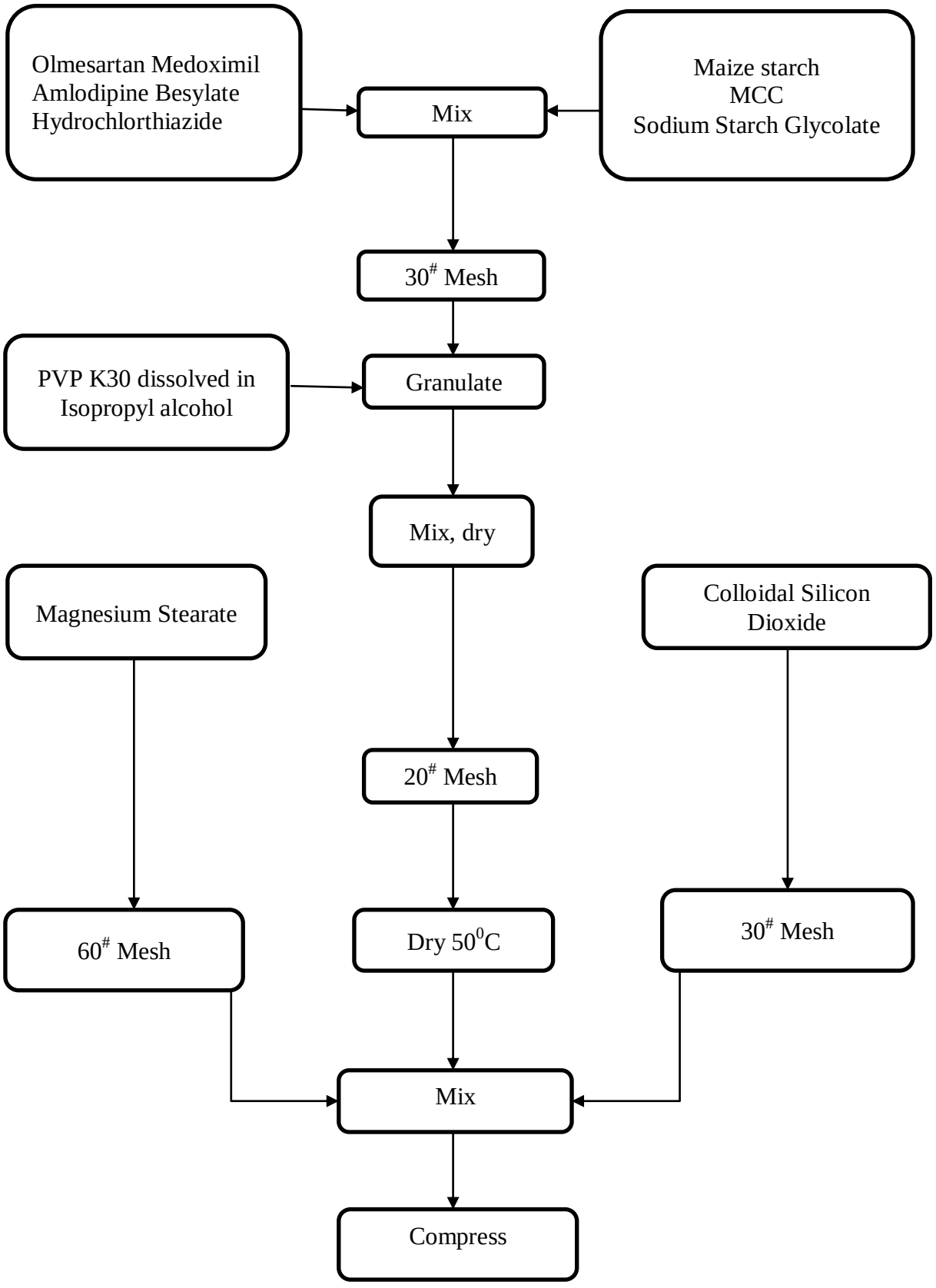
Raw material analysis of Hydrochlorthiazide was done as per IP. Identification test carried out by the Fourier Transform Infra-red spectrophotometer (FTIR). The report was shown in fig: 11.

7.2.5 Drug- Excipient Compatibility Study:

The drug and the excipients used for the formulation are screened for compatibility by physical compatibility study using FT-IR.

7.3 MANUFACTURING PROCESSES:

7.3.1 Flow chart 3: Wet Granulation Process:



7.3.2 Flow chart 4: Direct Compression Process:

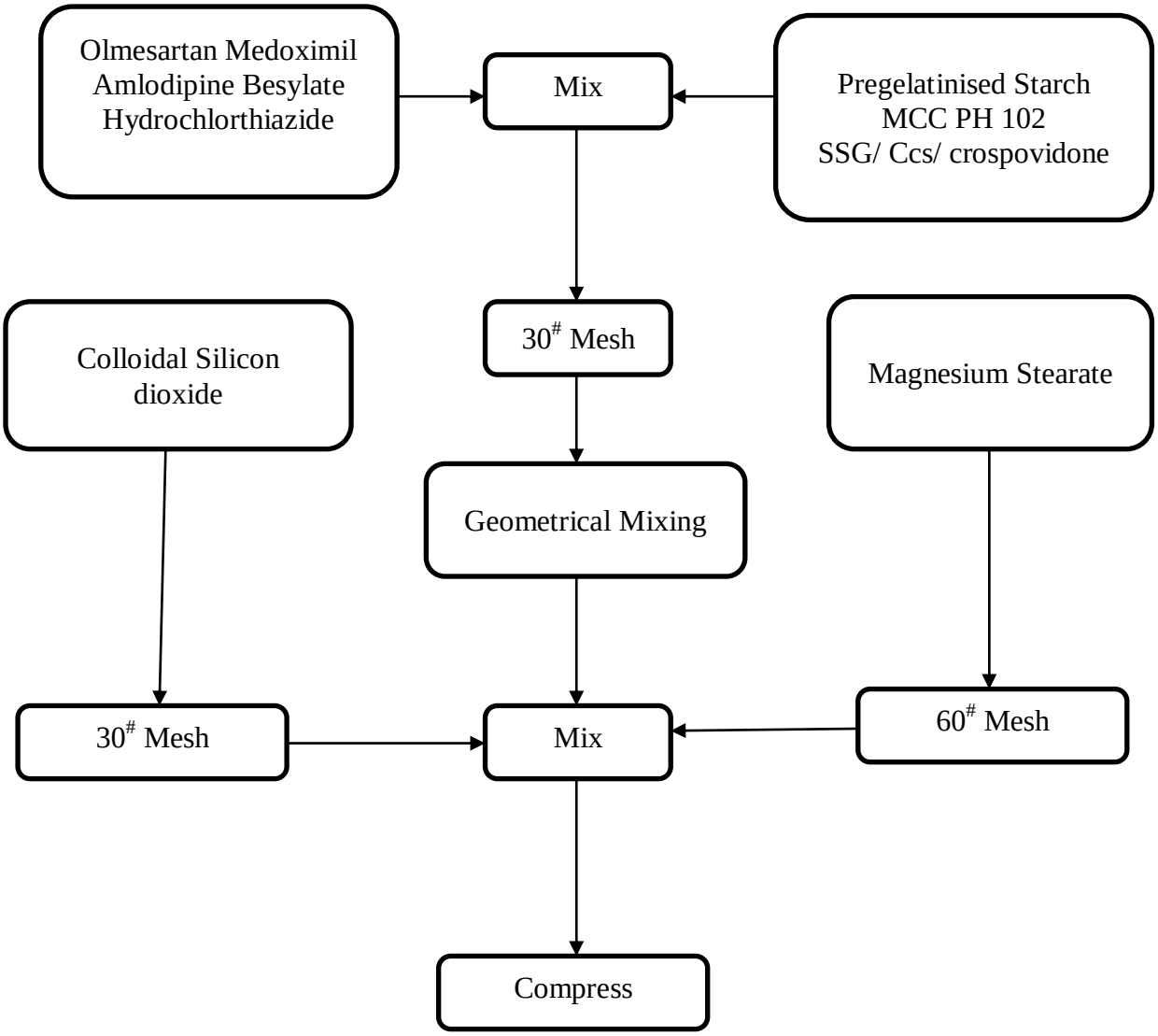


TABLE 10: FORMULATIONS

Materials	F1	F2	F3	F4	F5	F6	F7	F8
OLMESARTAN MEDOXOMIL	20	20	20	20	20	**20**	20	20
AMLODIPINE BESYLATE	7	7	7	7	7	**7**	7	7
HYDROCHLORTHIAZIDE	12.5	12.5	12.5	12.5	12.5	**12.5**	12.5	12.5
MAIZE STARCH	52.0	52.0	–	–	–	–	–	–
MCC	66.5	62.5	–	–	–	–	–	–
PVP K30	4.0	8.0	–	–	–	–	–	–
IPA	q.s.	q.s.	–	–	–	–	–	–
PREGELATINISED STARCH	–	–	23.0	48.0	70.50	**70.50**	70.50	70.50
MCC PH 102	–	–	100.5	75.5	50.0	**50.0**	50.0	50.0
CROS CARMELLOSE SODIUM		4.0	4.0	4.0	4.0	**9.0**	–	–
SODIUM STARCH GLYCOLATE	–	–	–	–	–	–	9.0	–
CROS POVIDONE	–	–	–	–	–	–	–	9.0
Lubrication								
COLLOIDAL SILICON DIOXIDE	2.0	2.0	2.0	2.0	2.0	**2.0**	2.0	2.0
MAGNESIUM STEARATE	1.00	1.00	1.0	1.0	1.0	**1.0**	1.0	1.0
Total Average weight	**170.0**	**170.0**	**170.0**	**170.0**	**170.0**	**170.0**	**170.0**	**170.0**

7.4 EVALUATION OF DRY BLEND[76,77]:

7.4.1 Angle of repose:

Angle of Repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

The angle of repose was measured by allowing the granules to flow over a graph sheet placed on a horizontal surface through a funnel kept at a certain height. The height of the heap and circumference of the base of heap was drawn on the graph sheet with a pencil and the radius of the circle was measured.

The angle of repose was calculated by using the formula given below.

$$\text{Angle of Repose } (\theta) = \text{Tan}^{1}(h/r)$$

where, h = height of pile

r = radius of the base of the pile

Table 11: Angle of repose

Angle of Repose	**Flow property**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

7.4.2 Bulk density determination :

Bulk density is the ratio of weight of the powder to the bulk volume occupied. Weighed quantity of the powder (W) was taken in a graduated measuring cylinder and volume (V_0) was measured and bulk density was calculated using the formula.

Bulk density = weight of powder/volume of powder

$$BD = W/V_0 \text{ g/ml}$$

7.4.3 Tapped density determination :

Weighed quantity of powder was taken in a graduated cylinder and the volume was measured (V_0). The graduated cylinder was fixed in the 'Tapped Densiometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tapings was less than 2%. The final reading was denoted by (V_f). The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.

$$\text{Tapped density (TD)} = \frac{W}{v} \text{ g/ml}$$

7.4.4 Carr's index :

Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics.

Table 12: Carr's index and corresponding flow properties:

Carr's Index (%)	***Flow***
5-15	Excellent
16-18	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

$$\text{Carr's Index} = \frac{(\text{Tapped Density} - \text{Bulk Density})}{\text{Tapped Density}} \times 100$$

7.4.5 Hausner ratio :

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The relationship between Hauser's ratio and flow property.

Table 13: Hausner ratio and corresponding flow properties

Hausner Ratio	Property
0-1.2	Free flowing
1.2-1.6	Cohesive Powder

Hausner ratio was calculated by using the formula.

Hausner ratio = tapped density/bulk density

Hausner ratio = v_f / v_o

Where v_f = initial volume

v_o = final volume

7.5 COMPRESSION:

7.5.1 For granulation process:

Compress the granules at 200.0 mg average weight in a rotary compression machine using 8.00 mm circular concave punch.

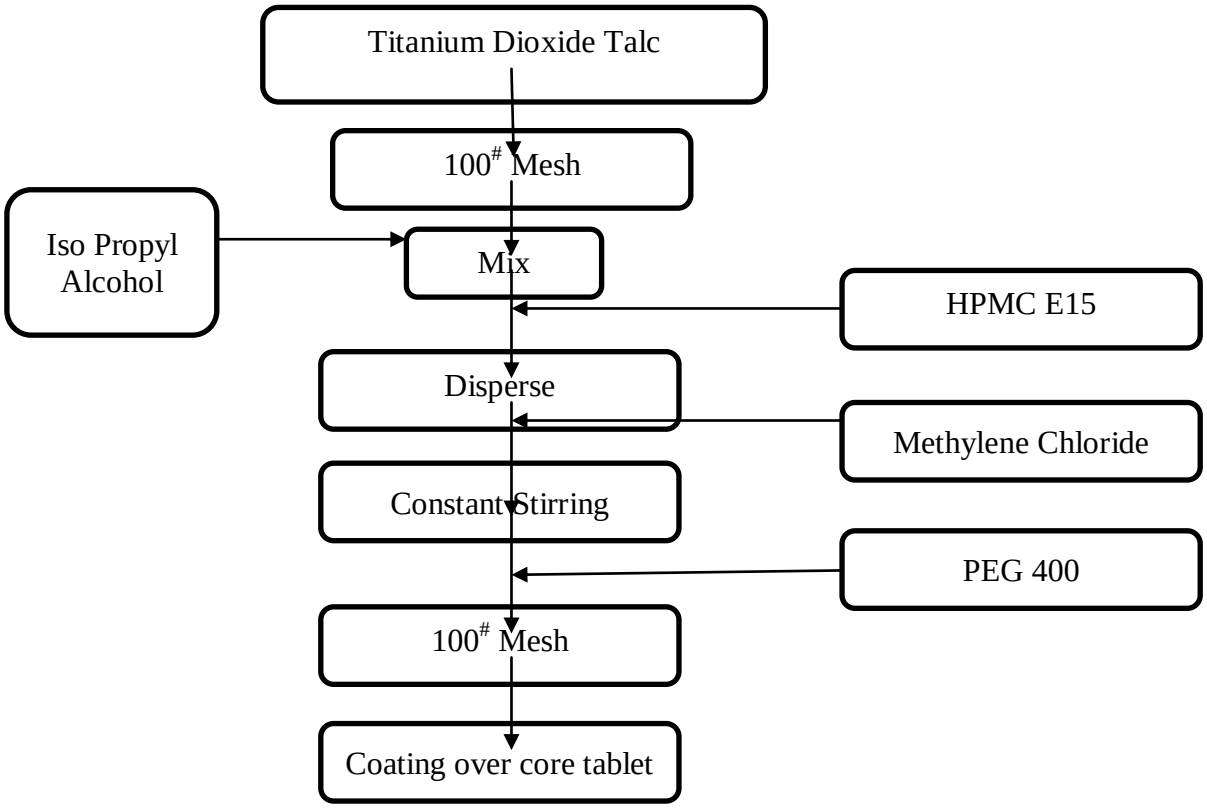
7.5.2 For direct compression process:

Compress the granules at 170.0 mg average weight in a rotary compression machine using 8.00 mm circular concave punch.

Table 14: Film coating formula

Ingredients	Quantity (mg/tab)
HPMC E15	5.1
Titanium dioxide	0.75
Talc	0.75
Isopropyl alcohol	35
PEG 400	0.5
Methylene chloride	100

FLOW CHART 5: Flow chart for film coating process:



7.7 EVALUATION OF TABLET[78]:

7.7.1 General appearance:

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters are shape, color, presence or absence of odor and taste were evaluated visually.

7.7.2 Uniformity of Weight:

Twenty tablets were selected at a random and weighed individually. The average weight was calculated. The percentage deviation of tablets was calculated and compared with the standard specifications.

Table 15: %deviation for average weight of tablet

S.No	Average weight of a tablets	% deviation
1	80 mg or less	±10
2	80 to 250 mg	±7.5
3	above 250 mg	±5

7.7.3 Thickness:

The thickness was measured to determine the uniformity of size and shape. Thickness of the tablets was measured using vernier caliper.

7.7.4 Hardness:

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations was determined using Dr. Schleuniger Pharmatron model 5Y tablet tester. It was expressed in kp.

7.7.5 Friability:

Friability of the prepared formulations was determined by using Roche friabilator. Pre- weighed sample of tablets was placed in the friability tester, which was then operated for 25 revolutions for 4 min, tablets were dedusted and

reweighed. The friability of the tablets was calculated using the formula mentioned below.

$$F(\%) = \frac{\text{initial weight-final weight}}{\text{initial weight}} \quad X100$$

7.7.6 Disintegration Time:

The test is conducted using a specially designed instrument known as disintegration apparatus. The apparatus employs a basket of six tubes with a base of metal sieve. A tablet is placed in each tube and is held in place.

In the six-tube assembly, six tablets are placed and the assembly is suspended using a hanger. On the hanger, hanging the six-tube are assembled and the assembly is moved in vertical motion in water or a buffer solution at a fixed speed of 28- 32 cycles/minute. The time for disintegration of each tablet is recorded.

7.7.7 ASSAY:

Chromatographic conditions:

Buffer solution	:	3.4g KH_2PO_4 dissolved in 100ml water. P^H adjusted to 3.0.
Mobile phase	:	buffer:acetonitrile
Column	:	Inertsil ODS 150×4.6mm, 5µm
Wave length	:	264nm
Injection volume	:	20 µl
Flow rate	:	1.0ml/min
Column temperature	:	30^0 c
Sample holder	:	10^0 c

Preparation of standard solution:

64mg of hydrochlorthiazide, 25mg of equivalent amlodipine besylate and 100mg of olmesartan medoximil is made upto 200ml with acetonitrile. Further dilute 10ml of this solution to 50ml with mobile phase.

Preparation of sample solution:

Transfer 5 intact tablets into 200ml volumetric flask, add 10ml of water to disperse them and add 150ml of acetonitrile to it. Sonicate to dissolve and make up

the volume with acetonitrile. Further dilute 10ml of this solution to 50ml with mobile phase.

Procedure:

Inject 20 µL portion of diluent. Perform replicate injections of standard preparation and one injection of each test preparation into the HPLC system ,record the chromatograms and measure the peaks response.

Calculation:

For Olmesartan Medoximil

$$= \frac{\frac{spl\ area}{std\ area}}{} \times \frac{std\ wt}{200} \times \frac{10}{50} \times \frac{200}{spl\ wt} \times \frac{50}{10} \times \frac{Avg\ wt}{LC} \times \frac{std\ purity}{100} \times \frac{100-LOD}{100} \times 100$$

For Amlodipine Besylate

$$= \frac{\frac{spl\ area}{std\ area}}{} \times \frac{std\ wt}{200} \times \frac{10}{50} \times \frac{200}{spl\ wt} \times \frac{50}{10} \times \frac{Avg\ wt}{LC} \times \frac{purity}{100} \times \frac{100-LOD}{100} \times \frac{408.5}{567.1} \times 100$$

For Hydrochlorthiazide:

$$= \frac{spl\ area}{std\ area} \times \frac{std\ wt}{200} \times \frac{10}{50} \times \frac{200}{spl\ wt} \times \frac{50}{10} \times \frac{Avg\ wt}{LC} \times \frac{purity}{100} \times \frac{100-LOD}{100} \times 100$$

7.7.8 IN-VITRO DISSOLUTION STUDIES:

DISSOLUTION FOR HYDROCHLORTHIAZIDE AND AMLODIPINE:

Medium preparation : 6.8mg of KH_2PO_4 and 915mg of NaOH is dissolved in 1000ml water and the p^H is adjusted to 6.8 with 0.1N HCL or 0 .1N NaOH

Medium : 900ml, P^H 6.8, phosphate buffer.

Apparatus : USP-II (paddle)

Speed : 50 RPM

Time : 45min

Temperature : 37^0 c ± 0.5 ^{0} c

Preparation of standard solution:

70mg hydrochlorthiazide and 28mg equivalent of amlodipine besylate and 110mg of olmesartan medoximil are added to 100ml volumetric flask and acetonitrile is added and further volume is made up with acetonitrile. Further 2ml of this solution is diluted to 100ml with dissolution medium.

Calculation:

For Amlodipine Besylate

$$= \frac{\text{spl area}}{\text{std area}} \times \frac{\text{std wt}}{100} \times \frac{2}{100} \times \frac{900}{1} \times \frac{1}{LC} \times \frac{\text{purity}}{100} \times \frac{100-LOD}{100} \times \frac{408.5}{567.1} \times 100$$

For Hydrochlorthiazide:

$$= \frac{\text{spl area}}{\text{std area}} \times \frac{\text{std wt}}{100} \times \frac{2}{100} \times \frac{900}{1} \times \frac{1}{LC} \times \frac{\text{purity}}{100} \times \frac{100-LOD}{100} \times 100$$

DISSOLUTION MEDIUM FOR OLMESARTAN MEDOXIMIL:

Medium : 900ml 0.1N HCl

Apparatus : USP-II Paddle type

Speed : 50 RPM

Time : 45min

Temperature : 37^0 C ± 0.5 ^{0} c

Preparation of standard solution:

110mg of olmesartan medoximil is added to 100ml acetonitrile. Further, 2ml of this solution is diluted to 100ml with dissolution medium.

Preparation of buffer:

3.4g KH_2PO_4 dissolved in 100ml water. P^H adjusted to 3.0.

For Olmesartan Medoximil:

$$= \frac{\text{spl area}}{\text{std area}} \times \frac{\text{std wt}}{100} \times \frac{2}{10} \times \frac{900}{1} \times \frac{1}{LC} \times \frac{\text{Std purity}}{100} \times \frac{100-LOD}{100} \times \frac{10}{0}$$

Chromatographic conditions for dissolution:

Mobile phase : Buffer:acetonitrile

Column : InertsilODS 150×4.6mm, 5µm

Wave length : 264nm

Injection volume : 50 µl

Flow rate : 1.0ml/min

Column temperature : 30^{0} c

Sample holder : 10^{0} c

7.8 Stability studies of formulation:

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F6 formulation was sealed in aluminium packaging laminated with polyethylene. Sample were kept at 25°C and 40°C and 75% RH for 1month. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics. The values were showed in the result.

RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION:

8.1 Identification of raw materials:

Olmesartan medoximil, amlodipine besylate and hydrochlorthiazide were subjected to following identification tests and the results shows that they have passed all the tests for identification and comply with the limits as per the monograph.

Table 16.0: Identification of raw materials:

	Olmesartan	Amlodipine	Hydrochlorthiazide
Description	white to off-white crystalline powder	white to off-white crystalline powder	White to almost white crystalline powder
Solubility	Insoluble in water. (sparingly soluble in strong acid, soluble in strong base, pH 3 to 9)	Slightly soluble in water, freely soluble in methanol; Sparingly soluble in anhydrous ethanol, slightly soluble in 2-orooanol.	Freely soluble in water, soluble in methanol, sparingly soluble in alcohol and slightly soluble in isopropyl alcohol
Melting point	175-180^{0}C	195 - 204 C	274 ^{0}C
Loss on drying	0.5% max	NMT 0.5%	NMT 1.0%

8.2 Calibration curves:

8.2.1 For Olmesartan medoximil:

Calibration curve of Olmesartan Medoximil was prepared. The calibration curve was linear between 2 to 20 µg/ml concentration ranges. The r^2 and slope were found to be 0.998 and 0.042.

Table 17.0: Calibration curve of Olmesartan Medoximil

Concentration (mcg/ml)	Absorbance
0	0
2	0.096
4	0.177
6	0.27
8	0.348
10	0.421

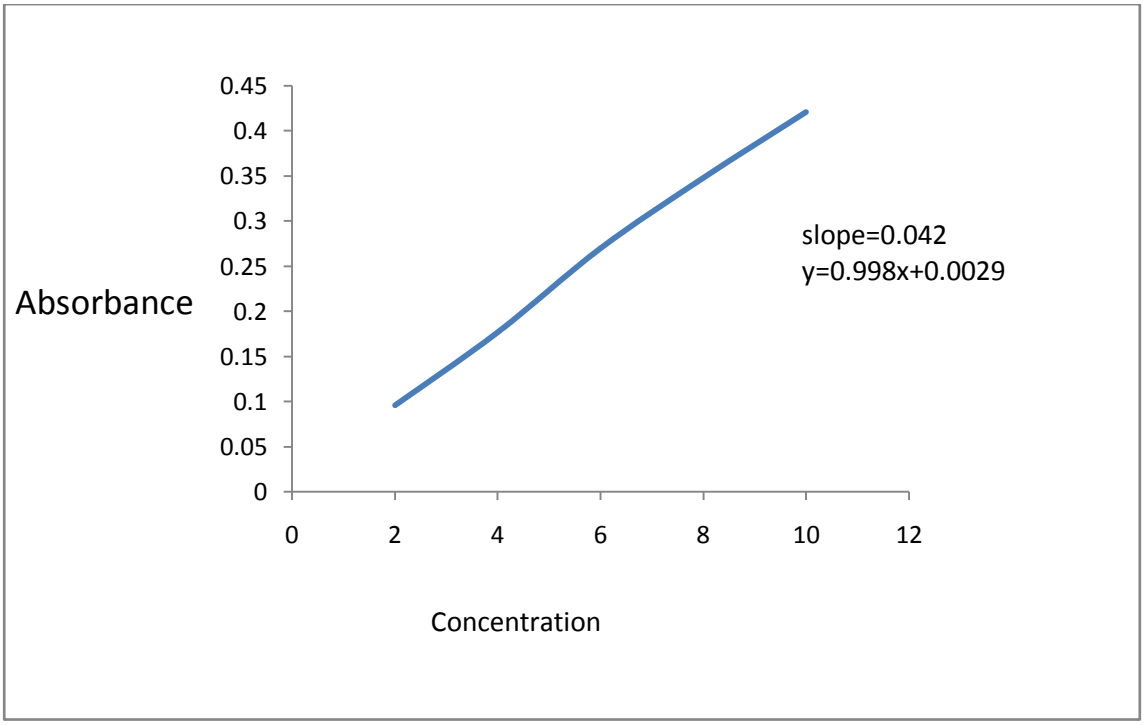


Figure 6. Concentration Vs Absorbance of Olmesartan Medoximil

8.2.2 For amlodipine besylate:

Calibration curve of Amlodipine Besylate was prepared. The calibration curve was linear between 2 to 20 µg/ml concentration ranges. The r^2 and slope were found to be 0.996 and 0.0323.

Table 18.0: Calibration curve of Amlodipine Besylate

Concentration(mcg/ml)	Absorbance
10	0.324
20	0.646
30	0.975
40	1.231
50	1.487

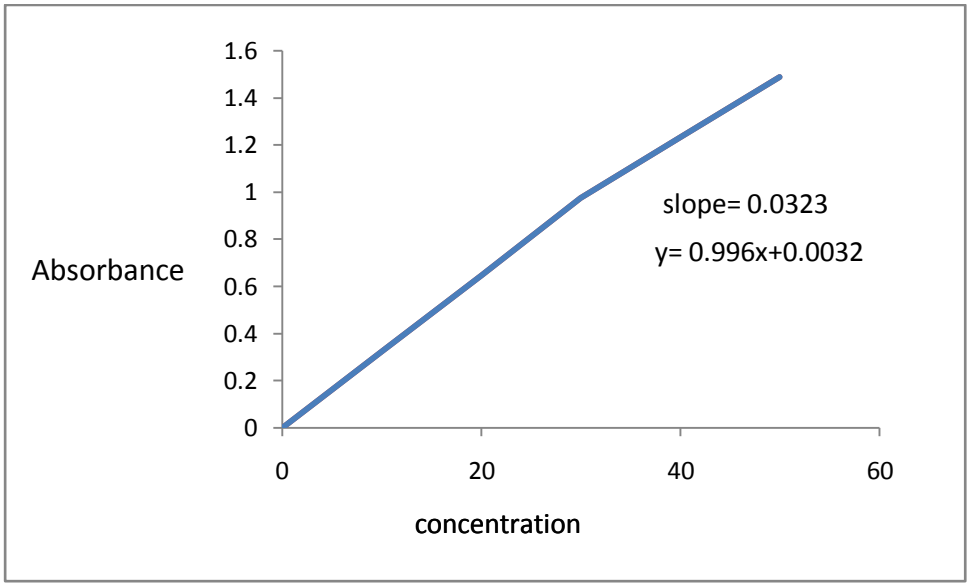


Figure 7: Concentration Vs Absorbance of Amlodipine Besylate

8.2.3 For Hydrochlorthiazide:

Calibration curve of Hydrochlorthiazide was prepared. The calibration curve was linear between 2 to 20 µg/ml concentration ranges. The r^2 and slope were found to be 0.989 and 0.012.

Table 19.0: Calibration curve of Hydrochlorthiazide

Concentration (mcg/ml)	Absorbance
0	0
10	0.156
20	0.211
30	0.362
40	0.487
50	0.639

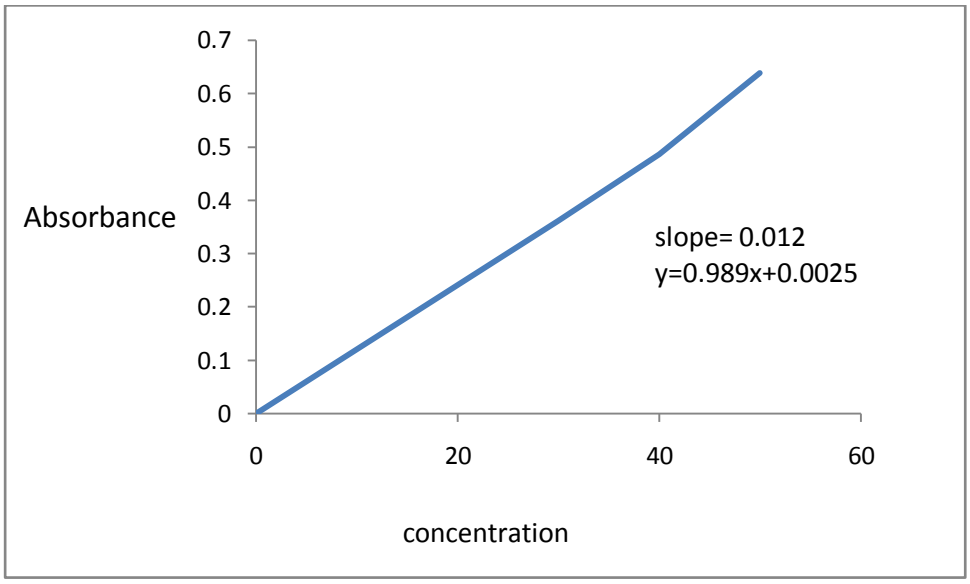


Figure 8: Concentration Vs Absorbance of Hydrochlorthiazide

8.3.1 Raw material analysis of Olmesartan Medoximil: The FT-IR spectrum for Olmesartan Medoximil is shown in the figure. It is done as per IP and is used for raw material analysis. The spectra show that the raw material obtained is pure.

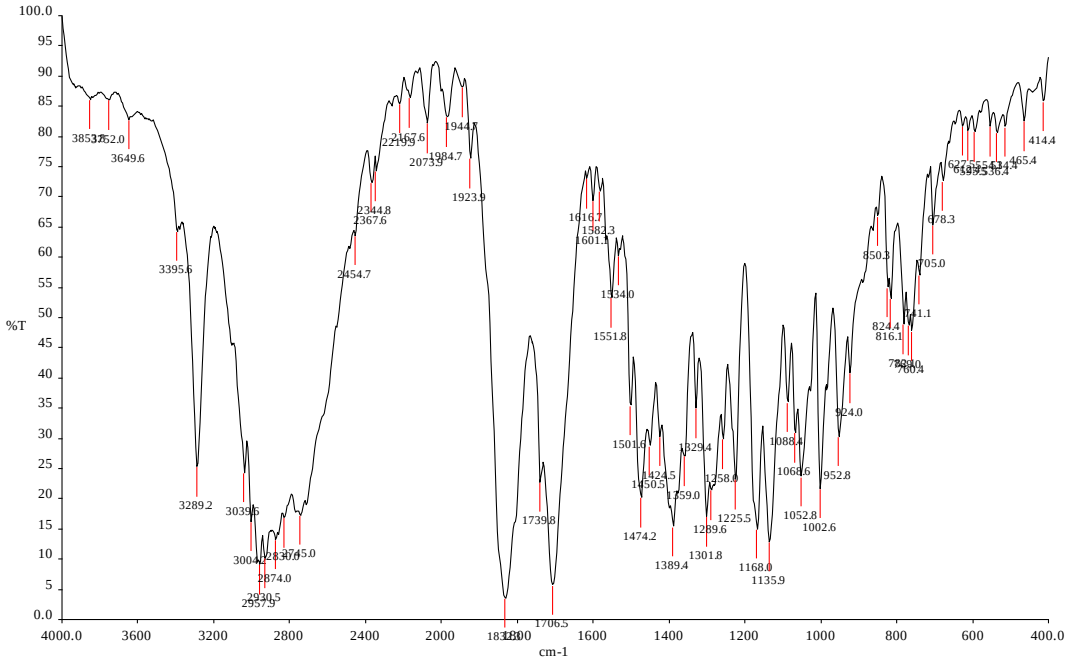


Figure 9: FT-IR Spectrum for Olmesartan Medoximil

8.3.2 Raw material analysis for Amlodipine Besylate:

The FT-IR spectrum for Amlodipine Besylate is shown in the figure. It is done as per IP and is used for raw material analysis. The spectra show that the raw material obtained is pure.

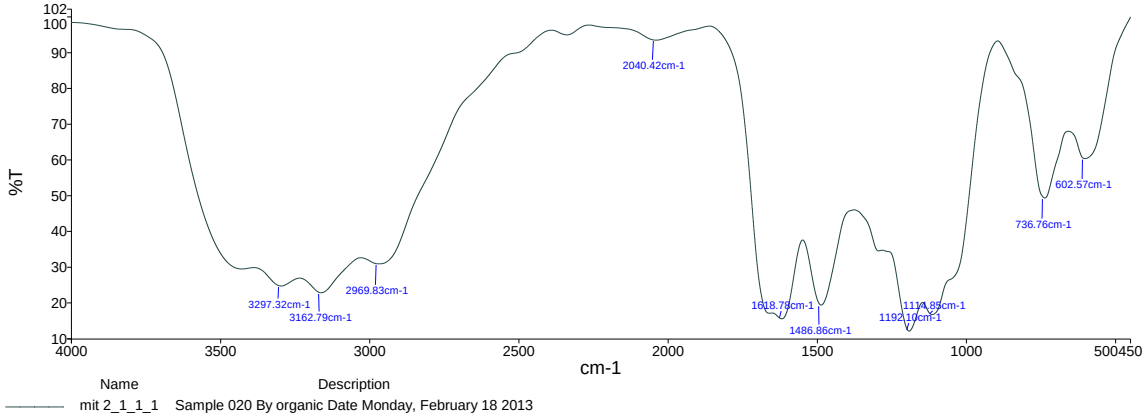


Figure 10: FT-IR Spectrum for Amlodipine Besylate

8.3.2 Raw material analysis for Hydrochlorthiazide:

The FT-IR spectrum for Hydrochlorthiazide is shown in the figure. It is done as per IP and is used for raw material analysis. The spectra shows that the raw material obtained is pure.

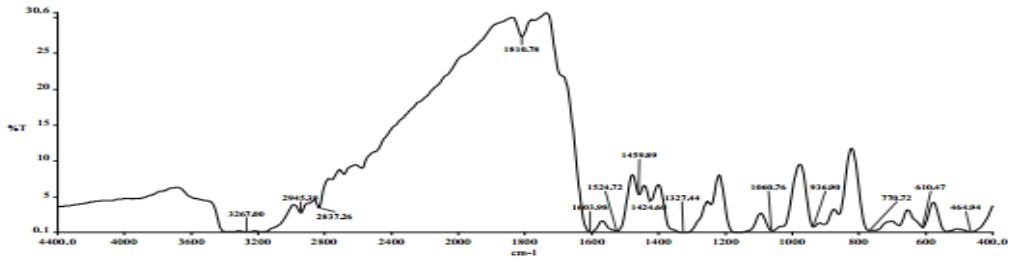


Figure 11: FT-IR Spectrum for Hydrochlorthiazide

8.4 Drug excipient compatibility study:

8.4.1 Spectrum for Olmesartan medoximil, Amlodipine Besylate and Hydrochlorthiazide (1:1:1):

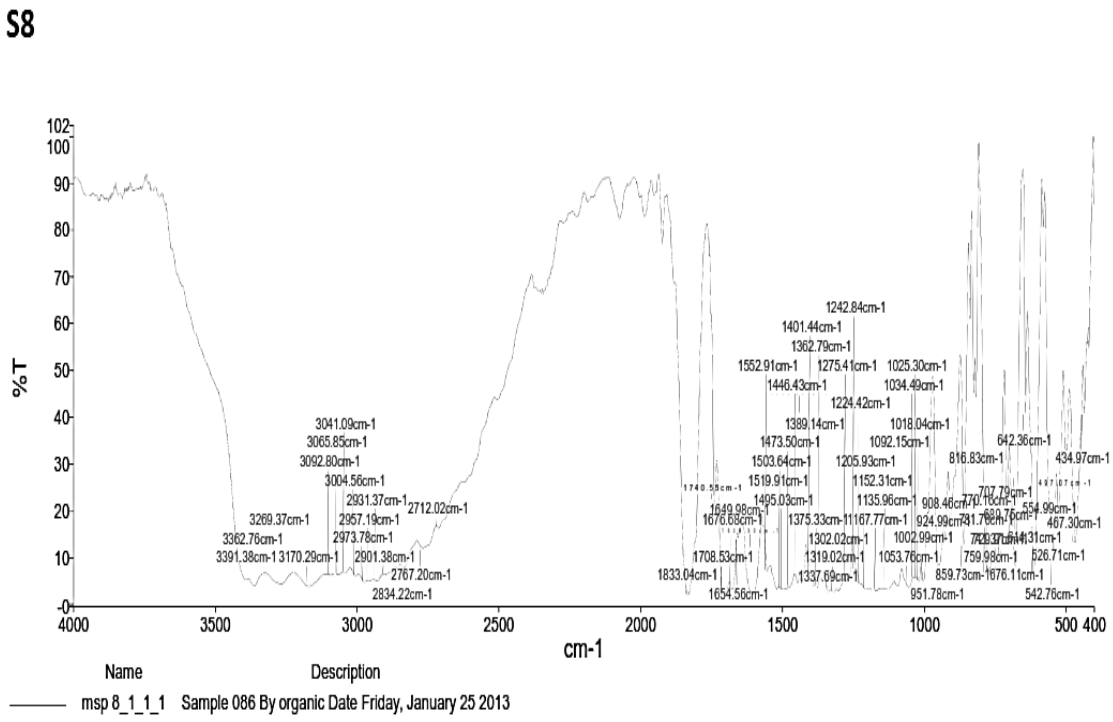


Figure 12: FT-IR Spectrum for 3 drugs (1:1:1)

8.4.2 Spectrum for Olmesartan Medoximil and Excipients:

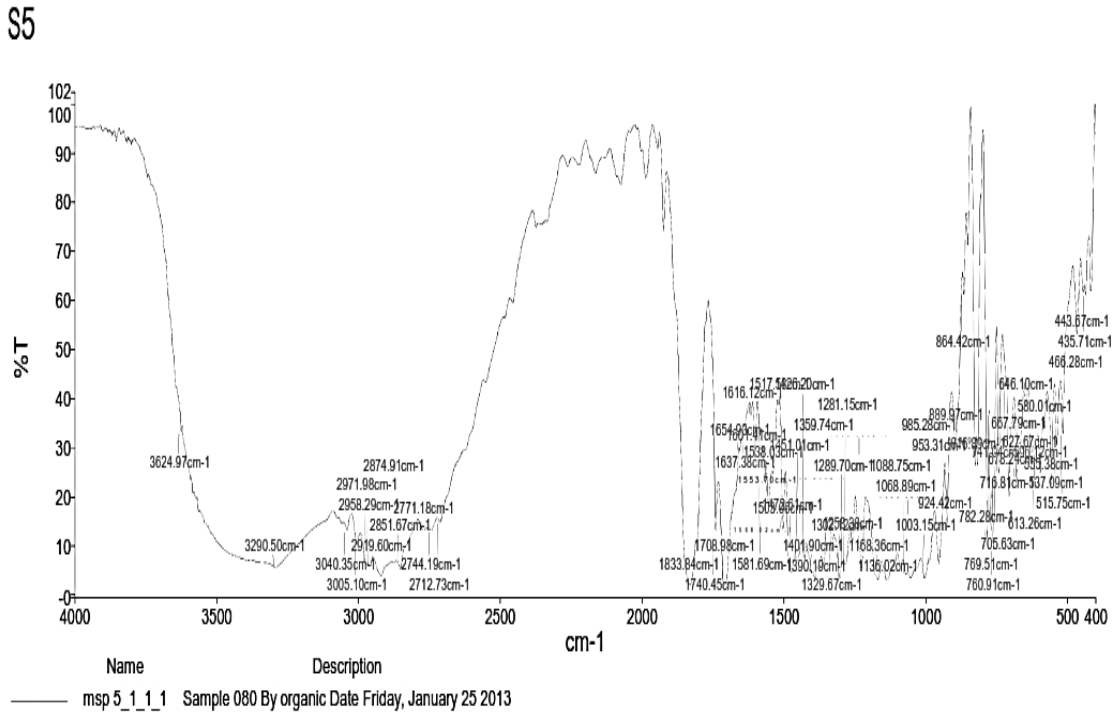


Figure 13: FT-IR Spectrum for Olmesartan Medoximil and excipients

8.4.3 Spectrum for Amlodipine Besylate and Excipients:

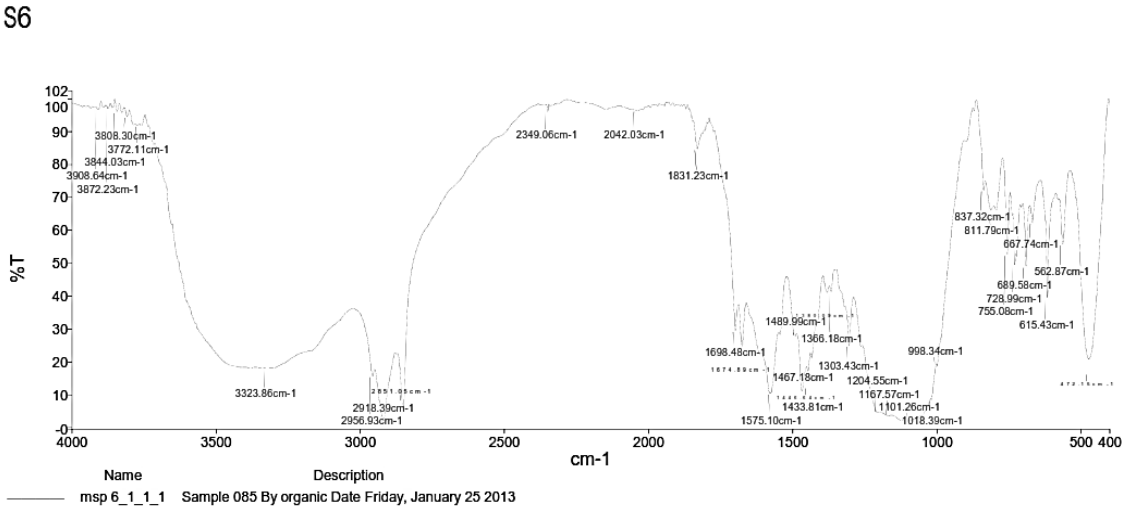


Figure 14: FT-IR Spectrum for Amlodipine Besylate and Excipients

8.4.4Spectrum for Hydrochlorthiazide and Excipients:

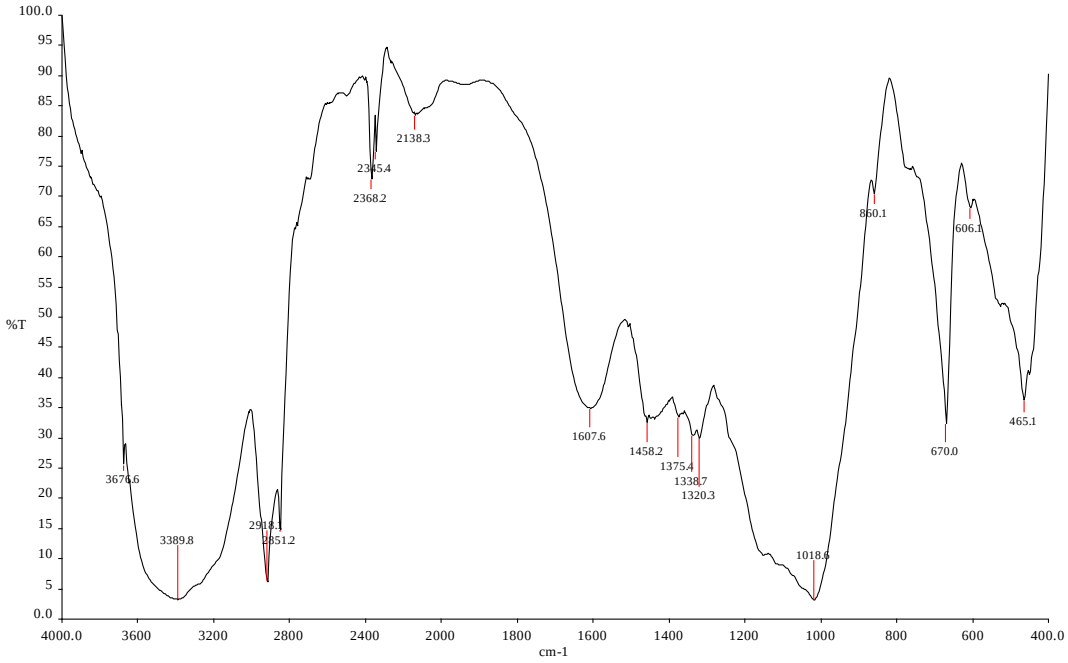


Figure 15: FT-IR Spectrum for Hydrochlorthiazide and Excipients

8.4.5 Spectrum of Olmesartan Medoximil, Amlodipine Besylate, Hydrochlorthiazide and Excipients:

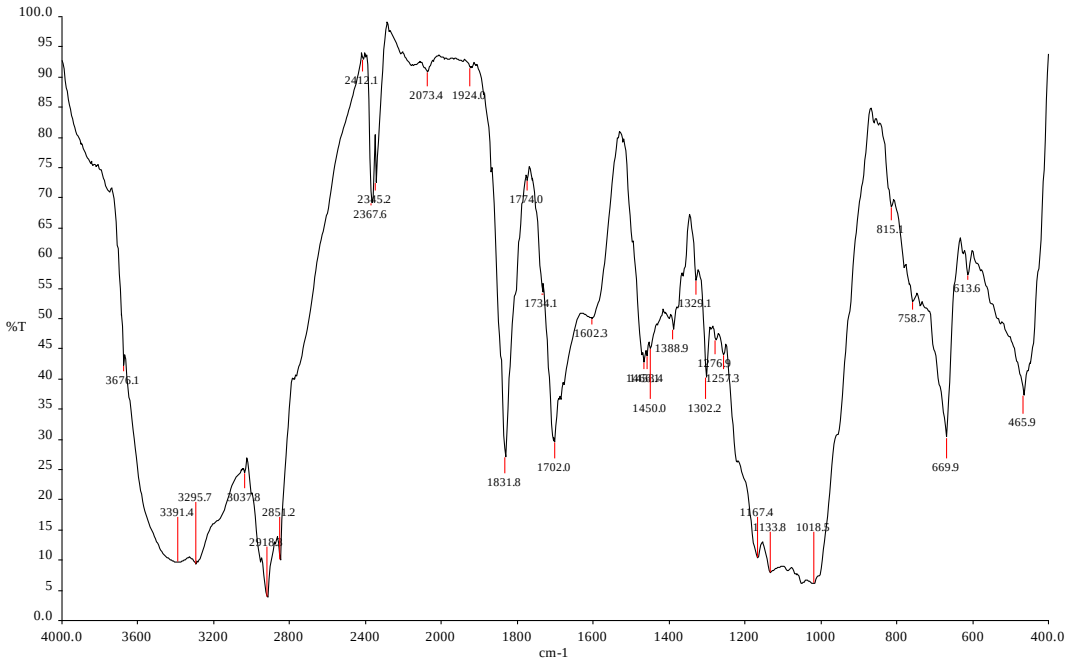


Figure 16: FT-IR Spectrum for 3 drugs (1:1:1) and Excipients

Interference: The FTIR spectra of the pure drugs are shown in the figure 5-12.The spectra of pure Amlodipine Besylate, Hydrochlorthiazide, Olmesartan Medoximil shows sharp characteristic peaks at 3230.19cm^{-1},1687.41cm^{-1},2971.75cm^{-1},1116.92cm^{-1}(Amlodipine) , 3370.26cm^{-1}, 1550.49cm^{-1}, 3170.20cm^{-1}, 1165.53cm^{-1}(Hctz) and 3395.6cm^{-1}, 1832.21cm^{-1},1551.81cm^{-1},1289.64cm^{-1} (Olmesartan) respectively. These peaks are also seen in the spectra of the physical mixtures containing the drug and excipients. This indicates there was no interaction between the drug and excipients.

.8.5 Evaluation of Dry Blend:

Table 20: Angle of Repose

s.no.	Formulations	Angle of repose (θ)
1.	F-1	27.3
2.	F-2	28.1
3.	F-3	39.4
4.	F-4	35.5
5.	F-5	31.2
6.	F-6	24.1
7.	F-7	27.8
8.	F-8	28.4

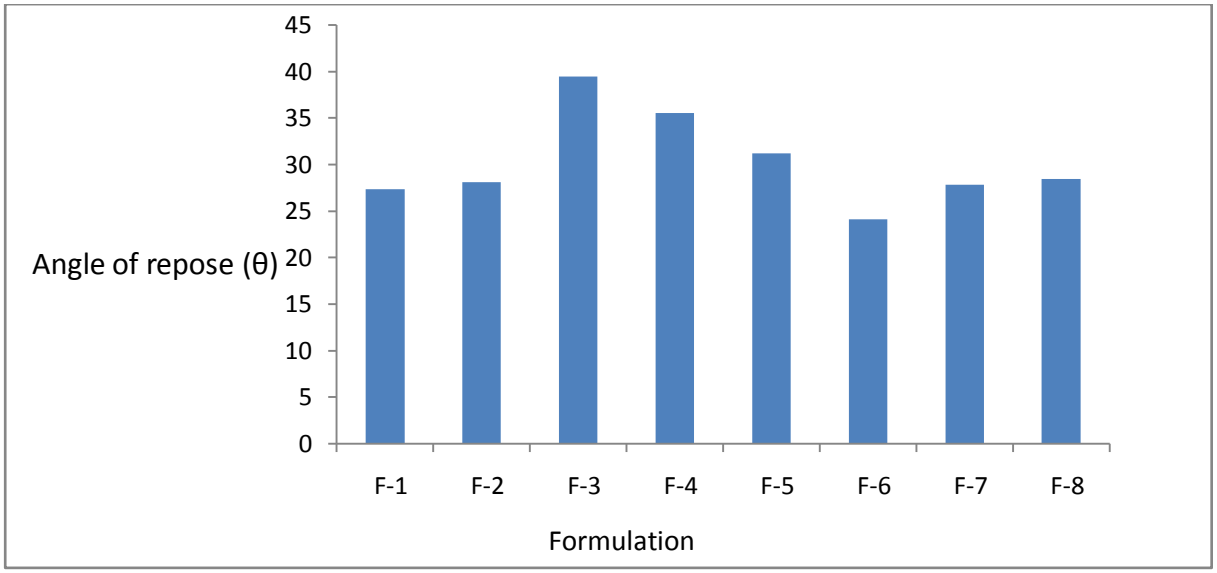


Figure 17: Evaluation of Angle of Repose

Table 21: Evaluation of granules/blend

s.no	Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's compressability Index %
1.	F-1	0.55	0.621	1.13	11.40
2.	F-2	0.581	0.643	1.11	16.52
3.	F-3	0.482	0.645	1.33	25.27
4.	F-4	0.491	0.571	1.16	14.01
5.	F-5	0.501	0.583	1.16	14.06
6.	F-6	0.528	0.596	1.13	11.40
7.	F-7	0.542	0.657	1.21	17.5
8.	F-8	0.573	0.653	1.13	12.25

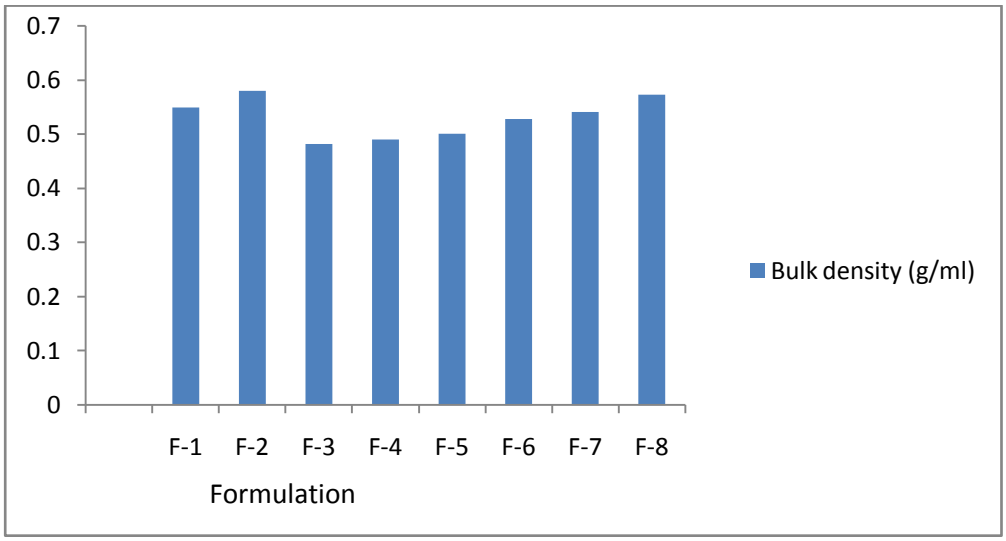


Figure 18: Evaluation of Bulk Density for various formulations

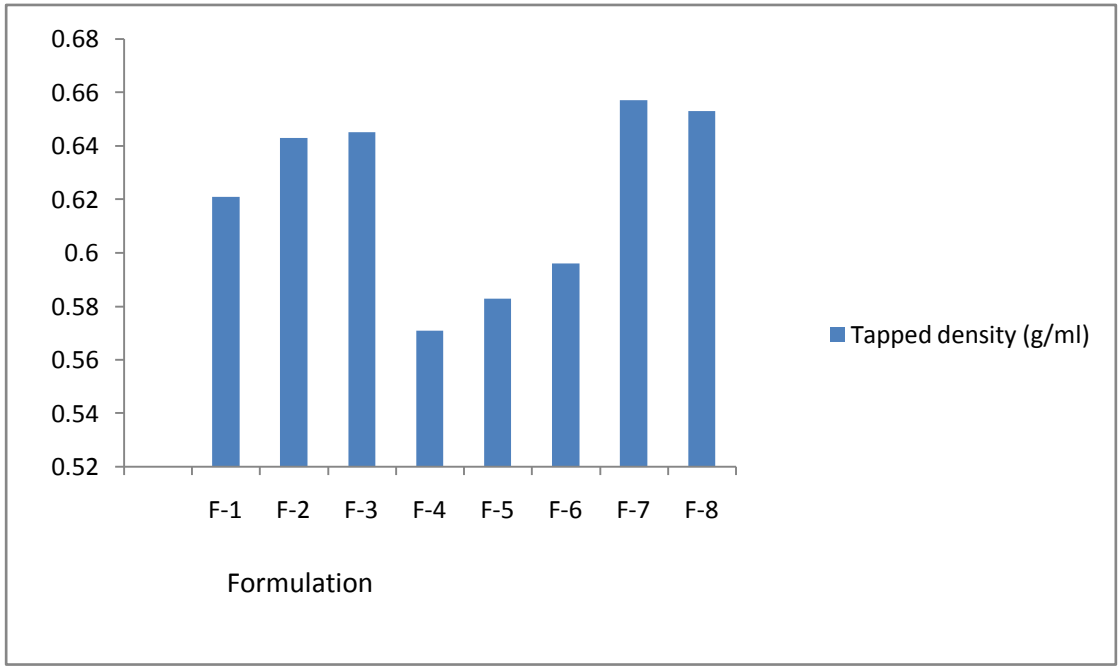


Figure 19: Evaluation of Tapped Density for various formulations

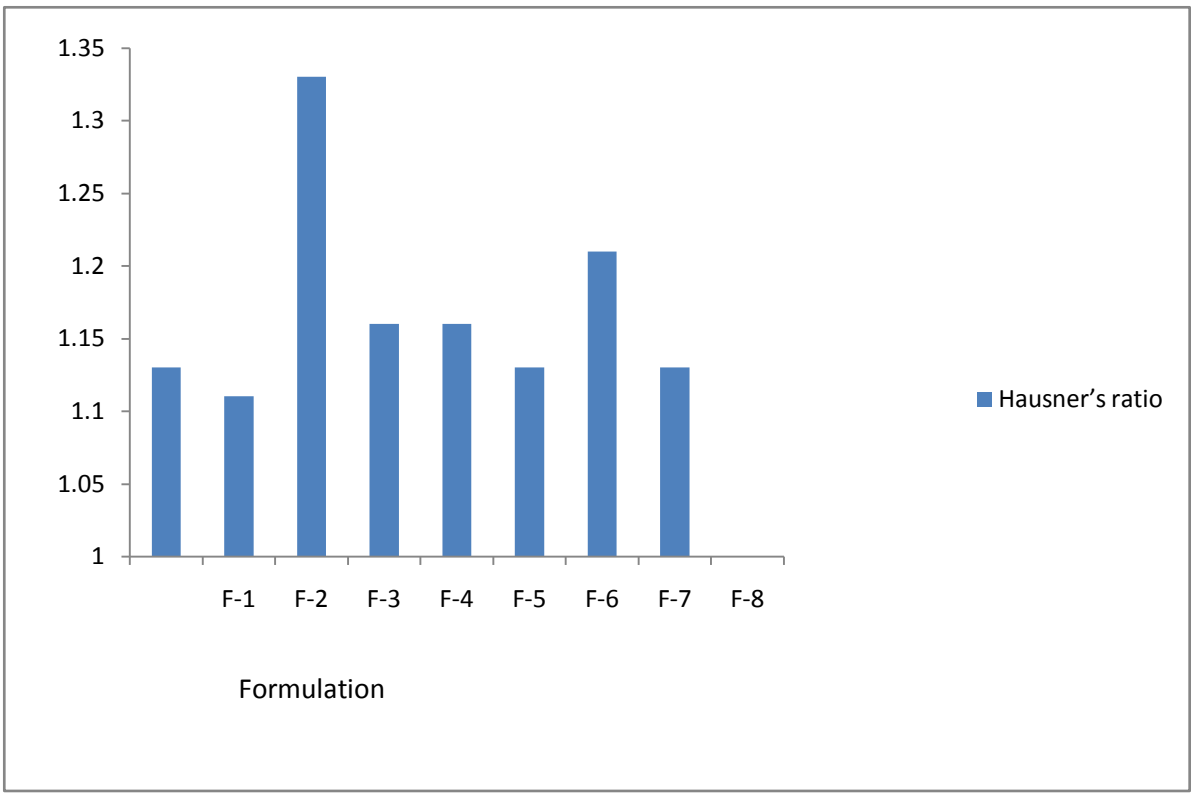


Figure 20: Evaluation of Hausner's Ratio for various formulations

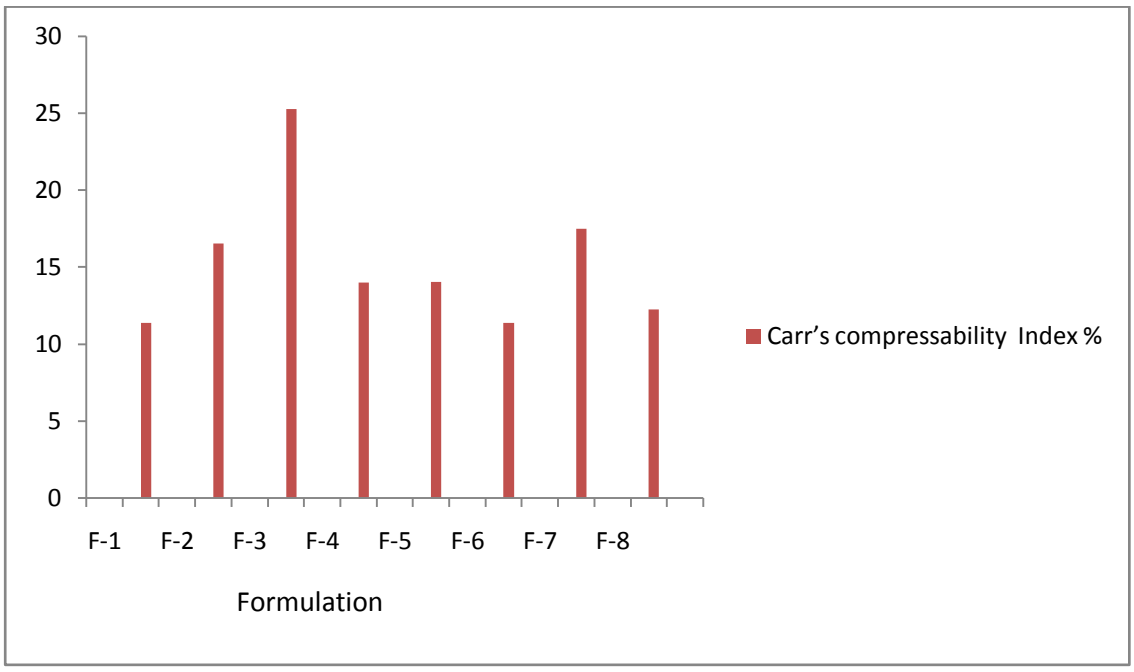


Figure 21: Evaluation of Carr's Index for various formulations

Inference:

- Angle of repose was found to be between $27^0.3$`- $41^06$`. Granules or blend possessing the range of less than 25 are considered to have an excellent flow property. The results were tabulated in table 17.0.
- Bulk density was found to be between 0.482-0.581. The results were tabulated in table 18.0
- Tapped density was found to be between 0.571-0.687. The results were tabulated in table 19.0
- Hausner's Ratio was found to be between 1.11-1.33.lower Hausner's Ratio (<1.25) indicate better flow compared to higher levels(>1.25). The results were tabulated in table 20.0
- Compressibility index was found to be between 11.40-25.27. Index between 5-15 shows excellent flow property. The results were tabulated in table 21.0.

8.6 Evaluation of tablet:

Table 22.0: Tablet Evaluation

Formulations	Average weight	Uniformity of weight	Thickness	Hardness	Friability	DT
F1	172.56mg	166- 175 mg	3.01 mm	2.0 kg/cm^2	1.14%	18m 45s
F2	172.20mg	168 – 175mg	3.05 mm	4.0 kg/cm^2	0.48%	14 m22s
F3	168.71mg	167-174mg	3.15mm	3.5 kg/cm^2	0.37%	7m 55s
F4	170.36mg	166-176mg	3.09mm	4.0 kg/cm^2	0.22%	7m 30s
F5	173.21 mg	167 – 175 mg	3.10 mm	4.5 kg/cm^2	0.17%	6m 55s'
F6	171.58 mg	165 – 173mg	2.98 mm	4.0 kg/cm^2	0.22%	3m 31s
F7	170.69 mg	168 – 175mg	3.03 mm	5.0 kg/cm^2	0.13%	5m 45s
F8	169.71 mg	166 – 173mg	3.06 mm	4.7 kg/cm^2	0.19%	5m 20s

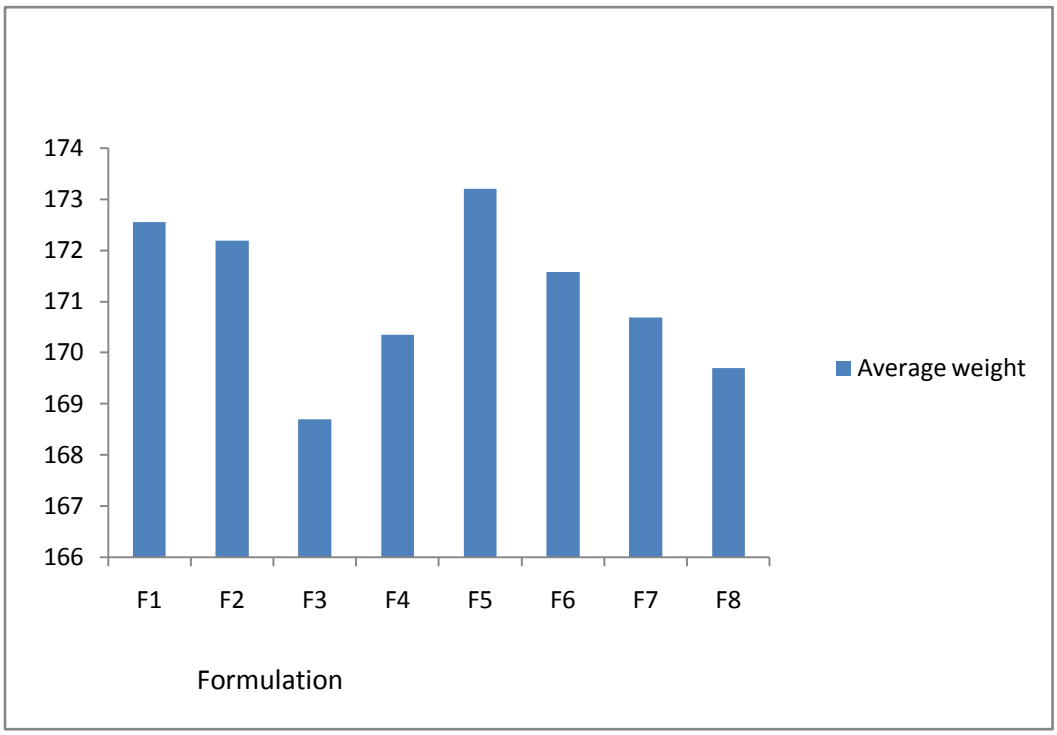


Figure 22: Evaluation of Average Weight of various formulations

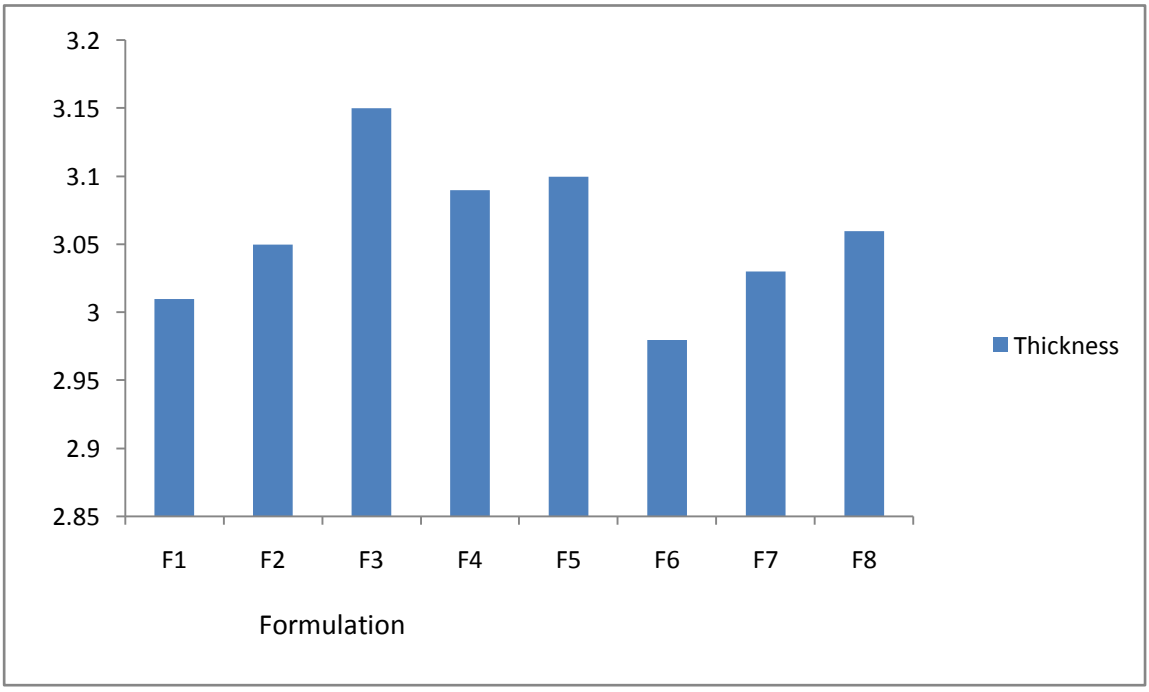


Figure 23: Evaluation of Thickness of various formulations

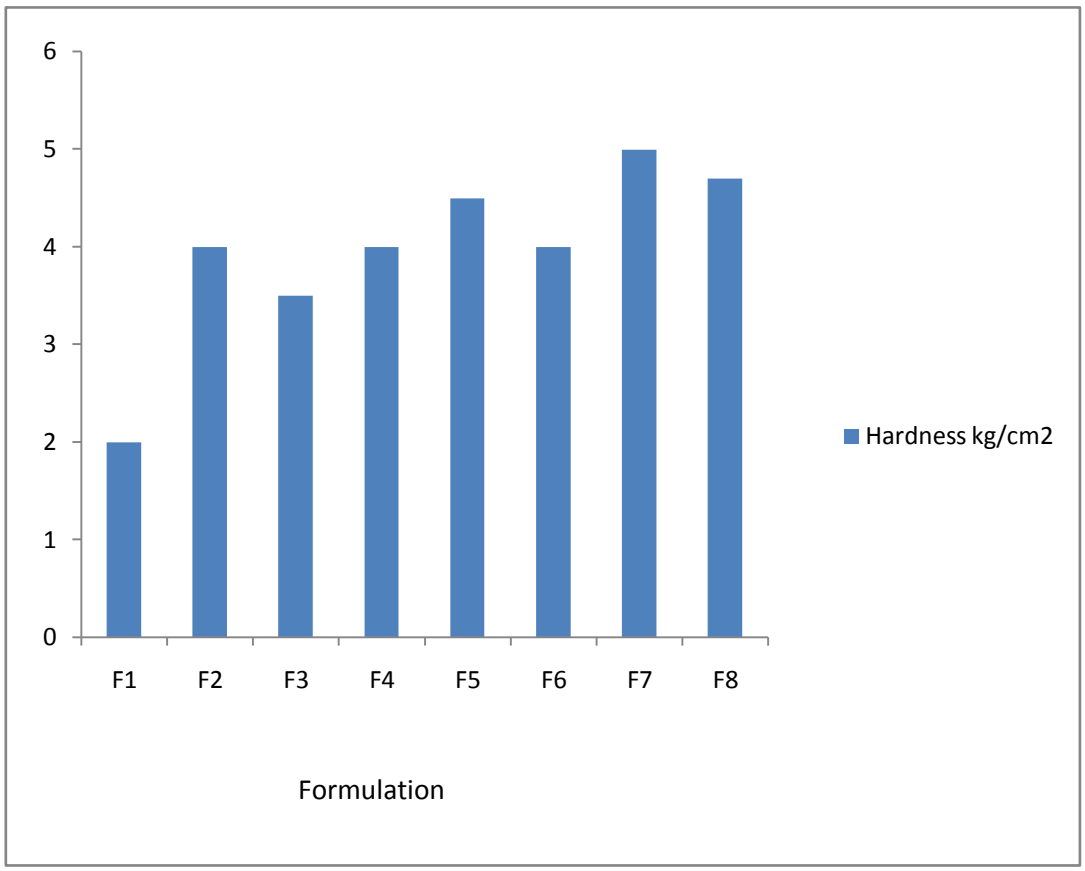


Figure 24: Evaluation of Hardness of various formulations

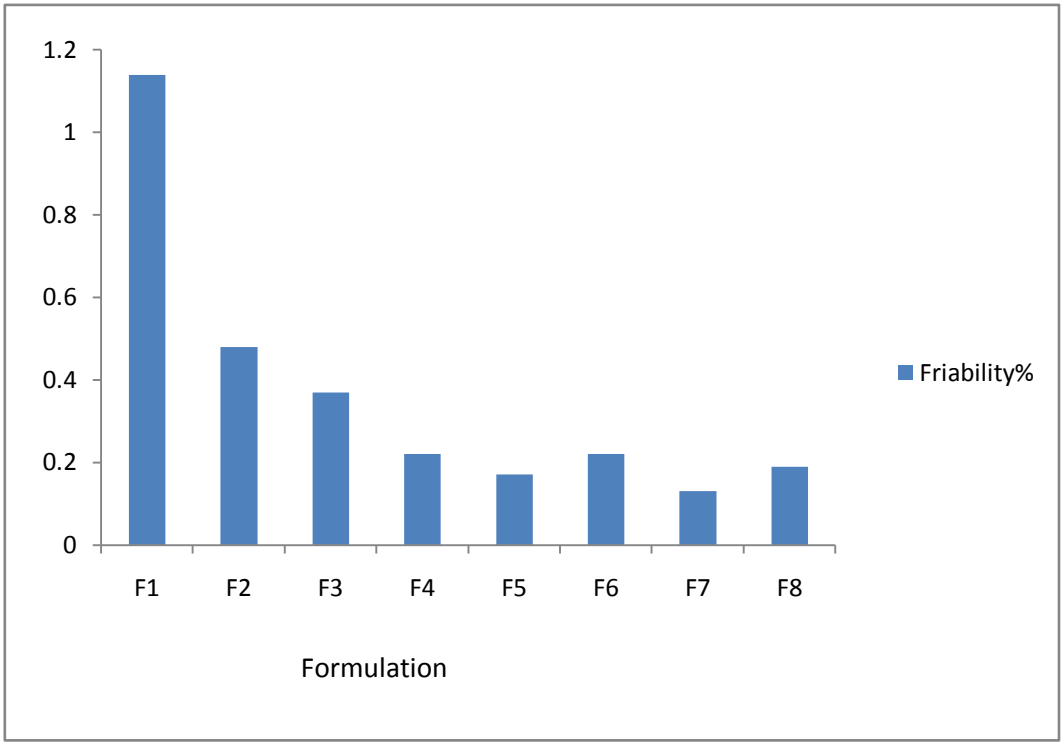


Figure 25: Evaluation of Friability of various formulations

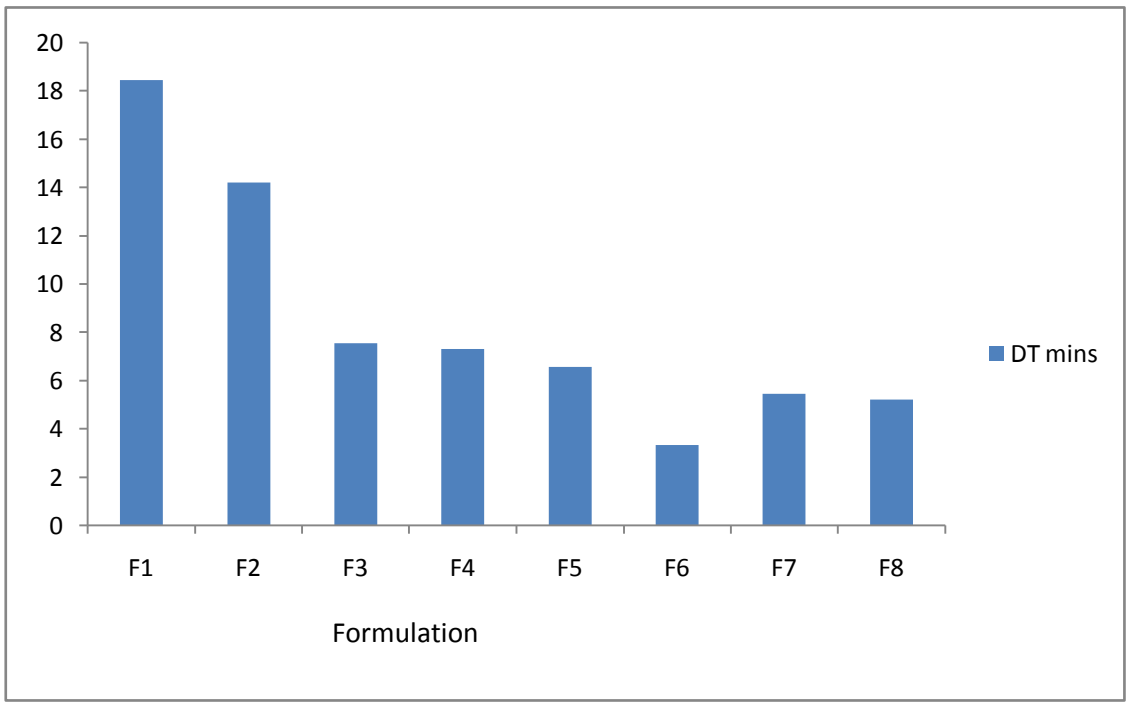


Figure 26: Evaluation of Disintegration time of various formulations

Inference:

- Eight formulations were prepared and designated as F-1, F-2, F-3, F-4, F-5, F-6, F-7 and F-8.
- Evaluation was carried out and the results were tabulated in table 22.
- Thickness of all formulations was found to be in range of 2.98-3.10. and thickness of all formulations is compared in figure 23.
- Hardness of all the formulations was found to be in range of 1.5-5 and hardness of all formulations is compared in figure 24.
- Friability of the formulations were observed to be in range of 0.13-1.34% and it is compared in figure 25.
- Uniformity of weight was observed to be within limits mentioned in I.P.
- Disintegration time was observed to be between 3.2 to 21.22 minutes and the DT for all formulations is compared in figure 26.

8.7 DRUG CONTENT:

Table 23: Drug content- olmesartan medoximil

s.no.	Formulations	Drug content (%)
1	F-1	94.34%
2	F-2	98.81%
3	F-3	96.23%
4	F-4	92.87%
5	F-5	98.12%
6	F-6	100.86%
7	F-7	98.95%
8	F-8	99.02%

Table 24.0: Drug content- amlodipine besylate

s.no.	Formulations	Drug content (%)
1.	F-1	93.56%
2.	F-2	98.23%
3.	F-3	94.12%
4.	F-4	96.12%
5.	F-5	92.34%
6	F-6	99.22%
7.	F-7	97.78%
8.	F-8	98.54%

Table 25.0: Drug content- hydrochlorthiazide

s.no.	Formulations	Drug content (%)
1.	F-1	98.23%
2.	F-2	94.44%
3.	F-3	97.17%
4.	F-4	92.47%
5.	F-5	95.19%
6.	F-6	101.76%
7.	F-7	99.80%
8.	F-8	98.98%

Table 26: In-vitro Dissolution profile

	F1	F2	F3	F4	F5	F6	F7	F8
olmesartan								
5	21.12	41.16	50.35	55.16	57.12	78.12	68.13	71.15
10	29.65	49.91	62.34	66.81	68.45	89.18	76.14	79.39
15	38.46	61.58	71.62	74.18	78.13	92.45	85.82	86.87
20	43.54	73.16	79.36	81.78	82.13	96.13	88.67	87.45
25	58.56	77.23	83.18	85.10	86.15	98.88	89.37	89.11
30	69.12	81.51	85.13	86.71	88.11	99.76	91.21	90.06
Amlodipine								
5	23.71	46.67	52.93	58.12	61.45	76.31	68.16	76.35
10	34.13	65.84	70.14	74.32	78.91	83.46	76.78	87.71
15	42.46	72.20	77.15	81.23	82.56	93.49	84.61	91.13
20	49.43	78.06	82.28	84.12	85.11	96.45	87.58	92.82
25	62.91	82.74	86.40	87.12	87.89	96.91	88.82	93.01
30	70.39	84.12	87.04	88.35	89.76	97.12	92.98	93.63
Hydrochlorthiazide								
5	26.71	48.67	54.17	61.23	69.82	76.05	73.95	79.58
10	33.75	59.80	72.36	73.12	79.67	86.72	87.07	85.71
15	46.13	74.53	79.14	82.56	85.94	94.90	91.52	88.90
20	52.92	81.42	82.31	85.51	88.50	97.67	92.67	90.38
25	60.19	82.91	84.16	86.78	89.16	98.14	92.99	91.62
30	68.12	84.45	85.87	87.91	90.79	98.37	93.53	92.45

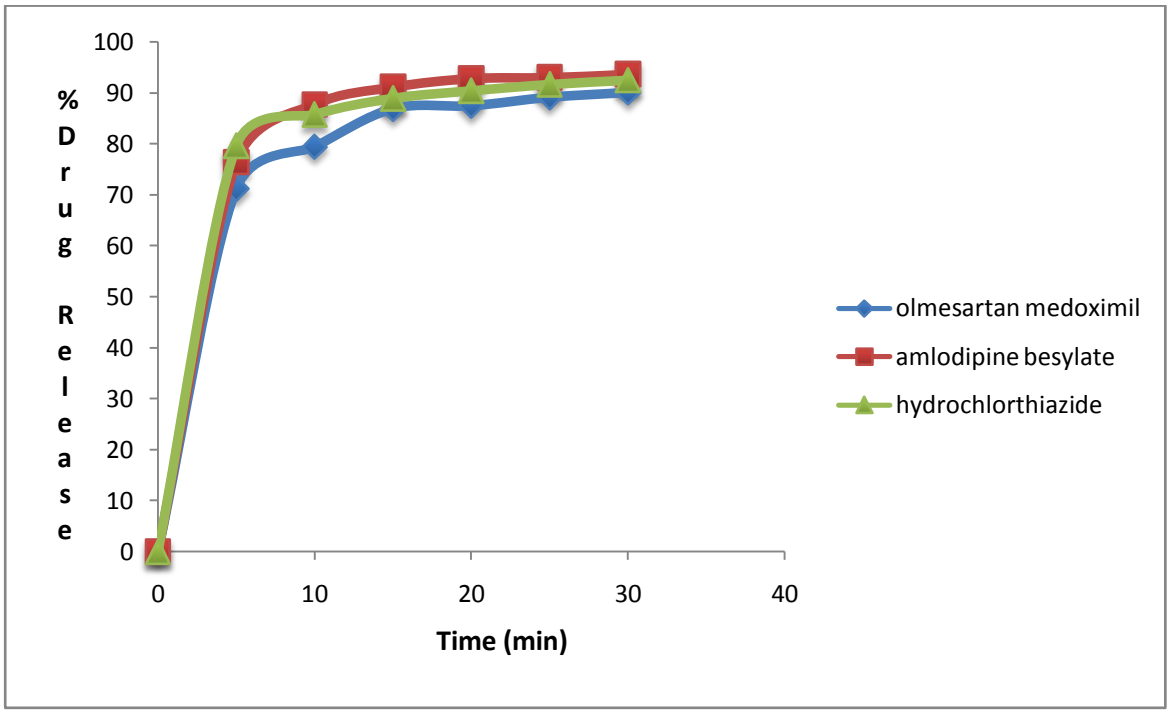


Figure 25: In-vitro dissolution profile for formulation F-1

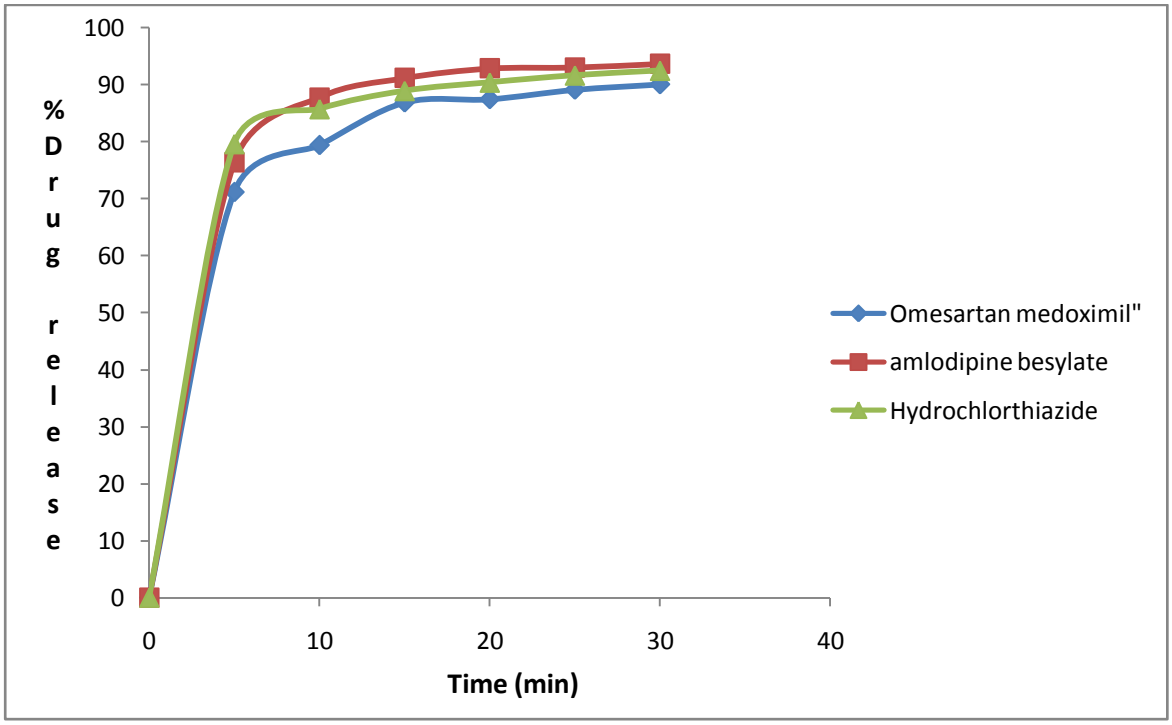


Figure 26: In-vitro dissolution profile for formulation F-2

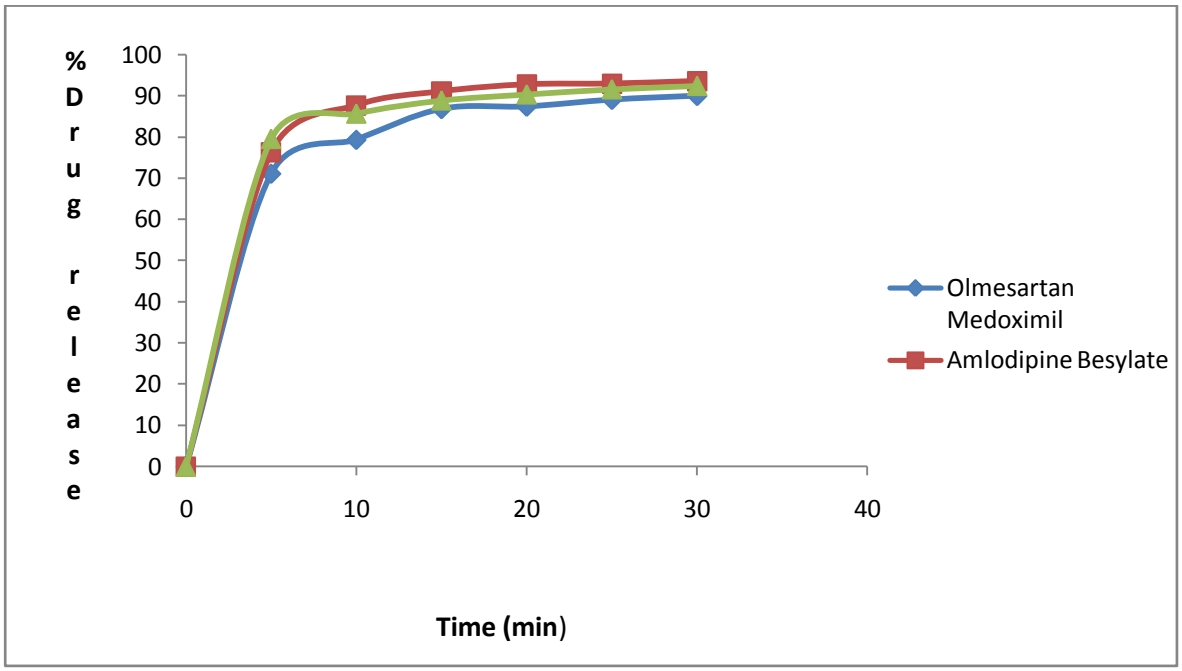


Figure 27: In-vitro dissolution profile for formulation F-3

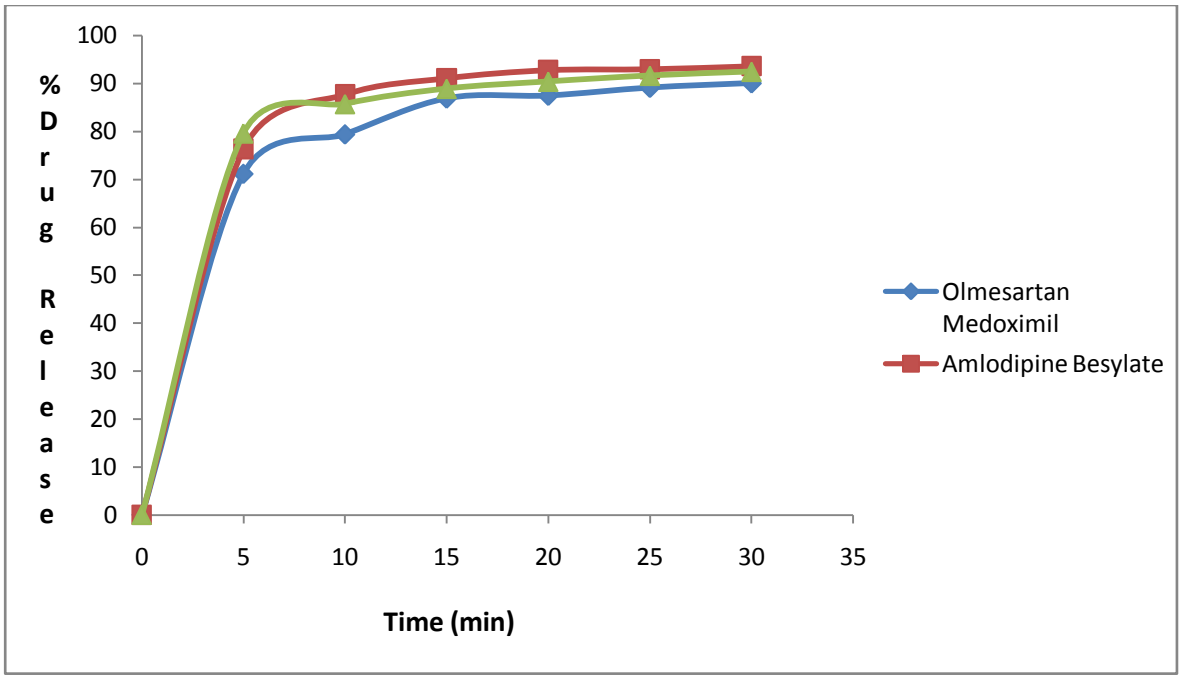


Figure 28: In-vitro dissolution profile for formulation F-4

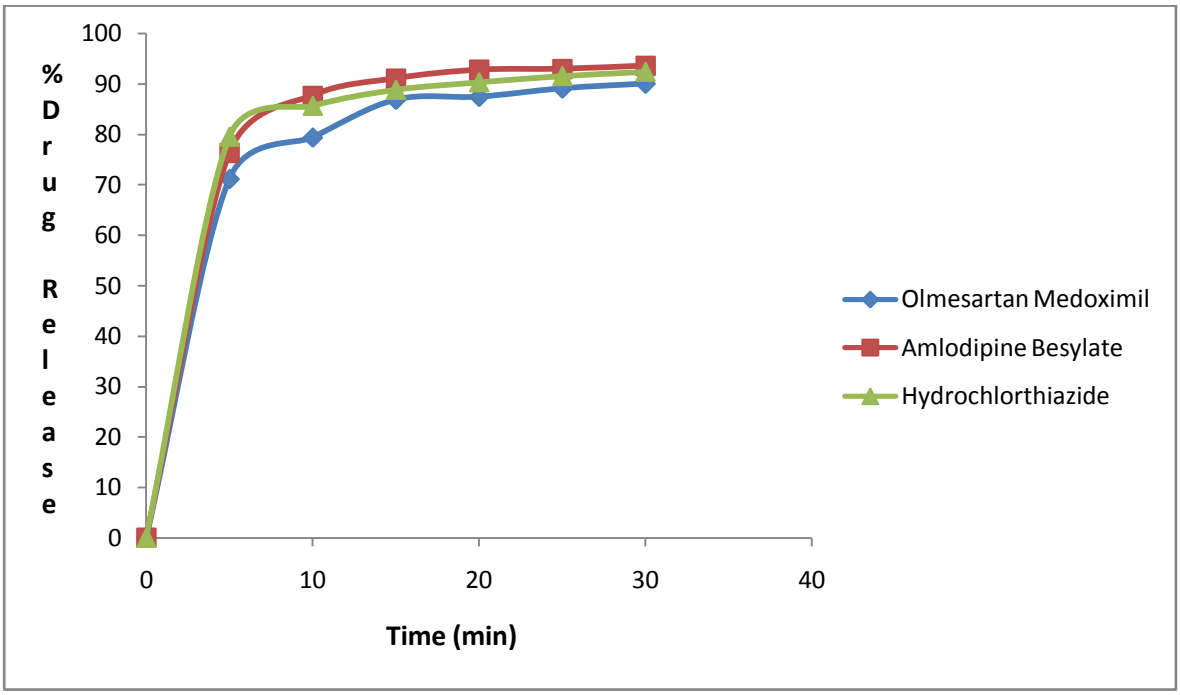


Figure 29: In-vitro dissolution profile for formulation F-5

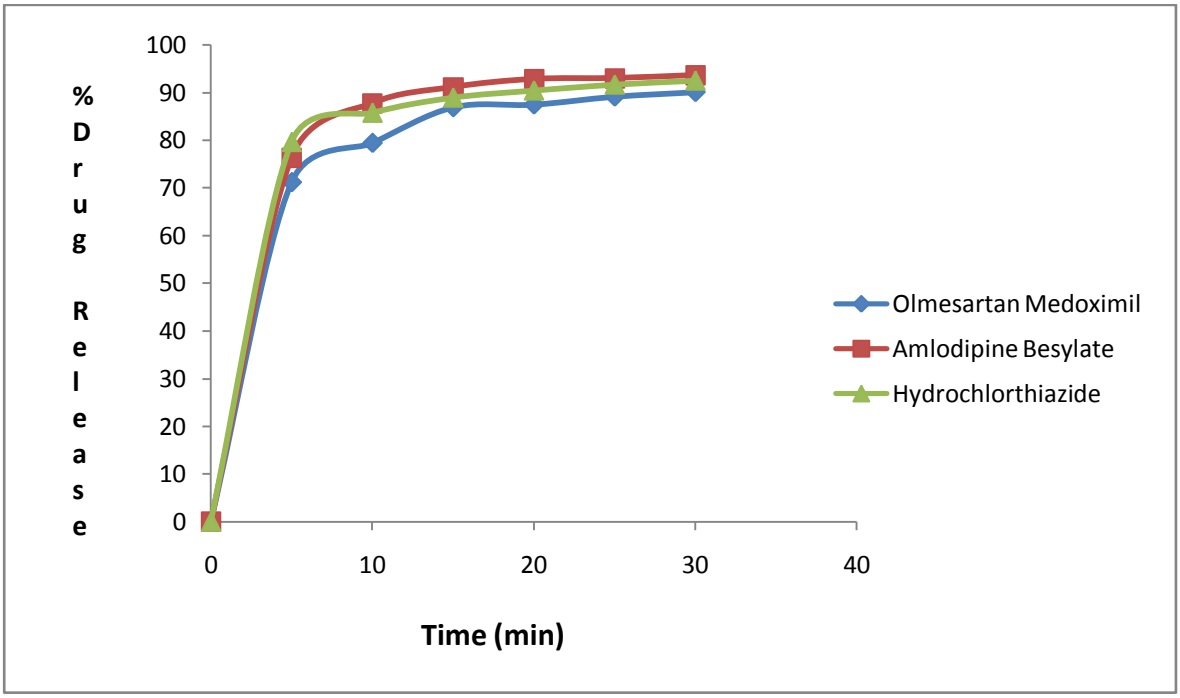


Figure 30: In-vitro dissolution profile for formulation F-6

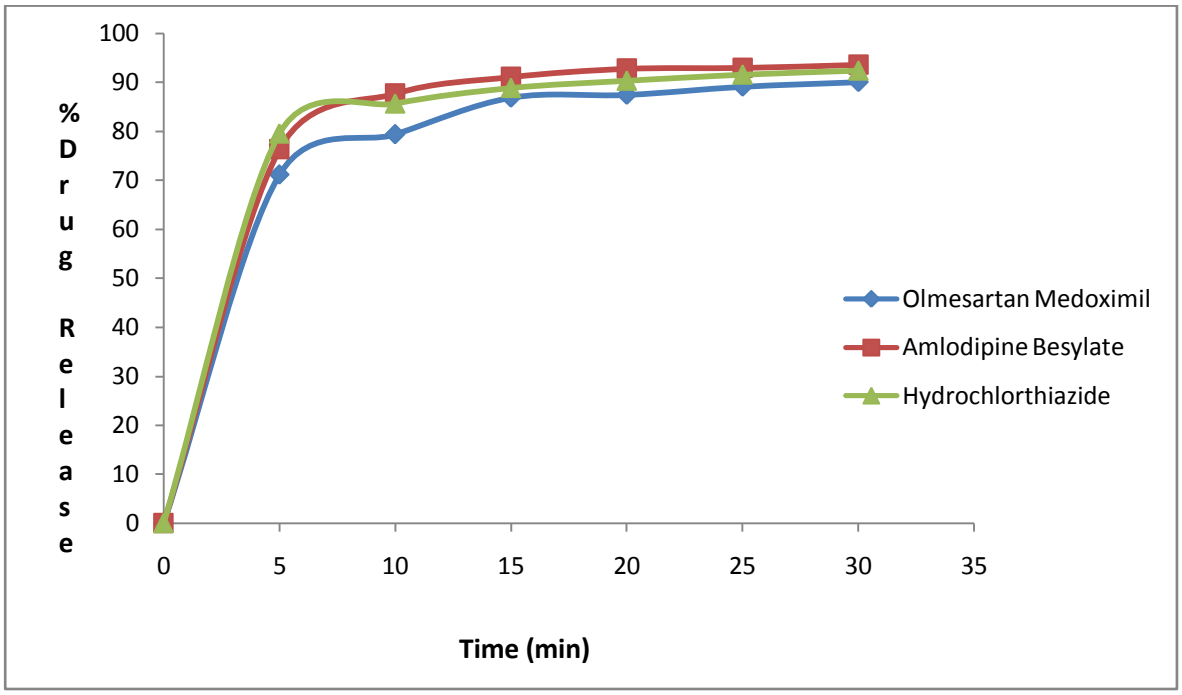


Figure 31: In-vitro dissolution profile for formulation F-7

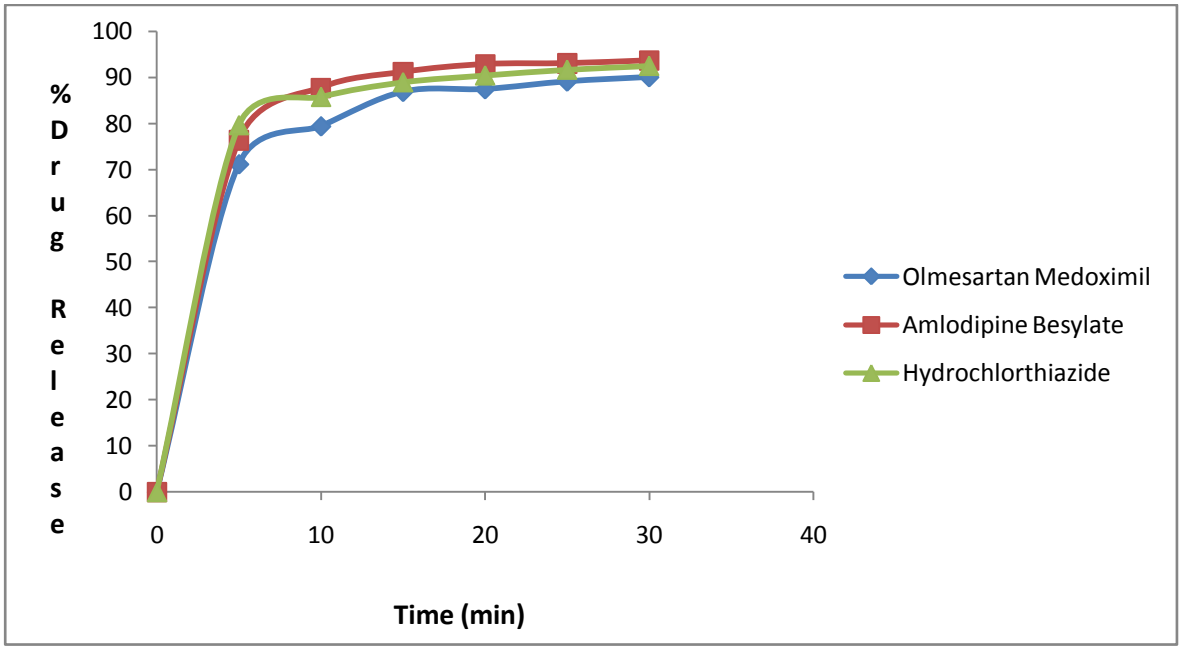


Figure 32: In-vitro dissolution profile for formulation F-8

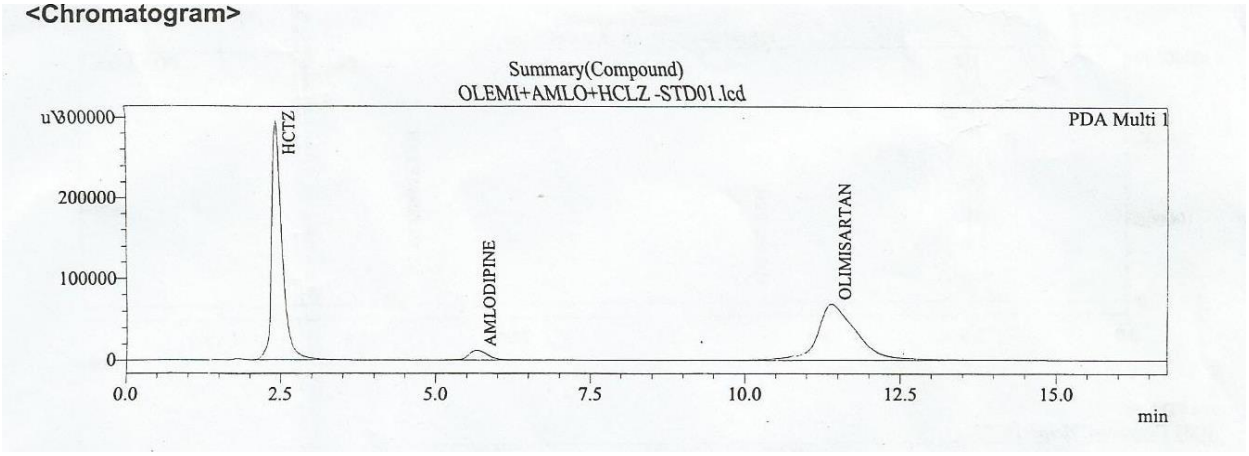


Figure 33: Chromatogram for standard

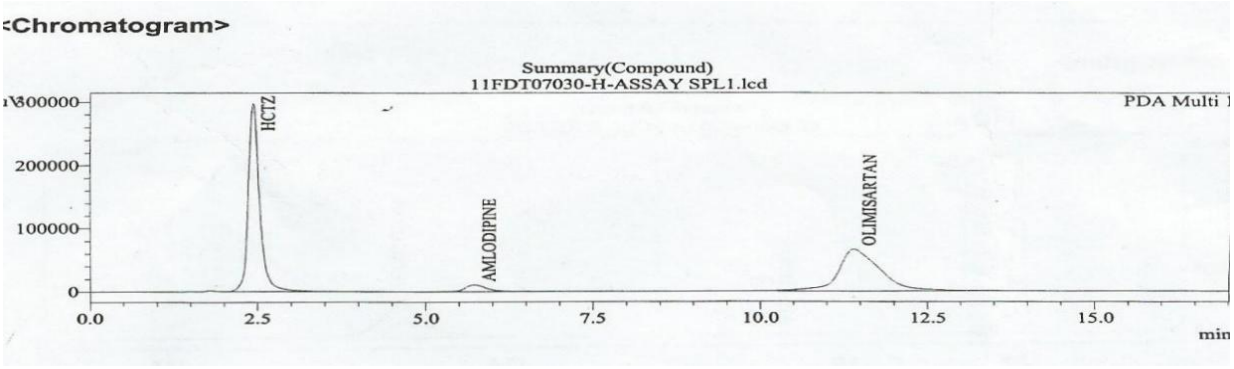


Figure 34: Chromatogram for sample

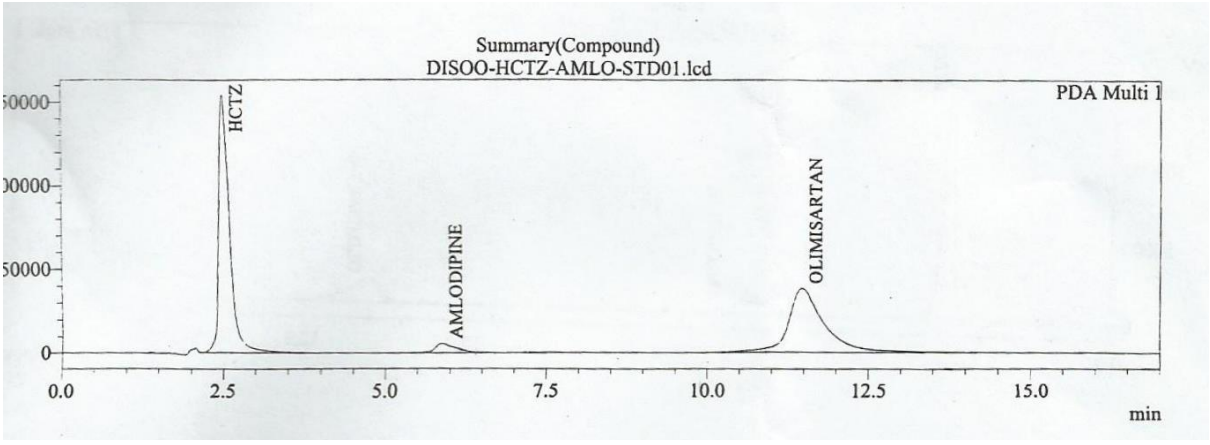


Figure 35: Dissolution chromatogram for standard 1

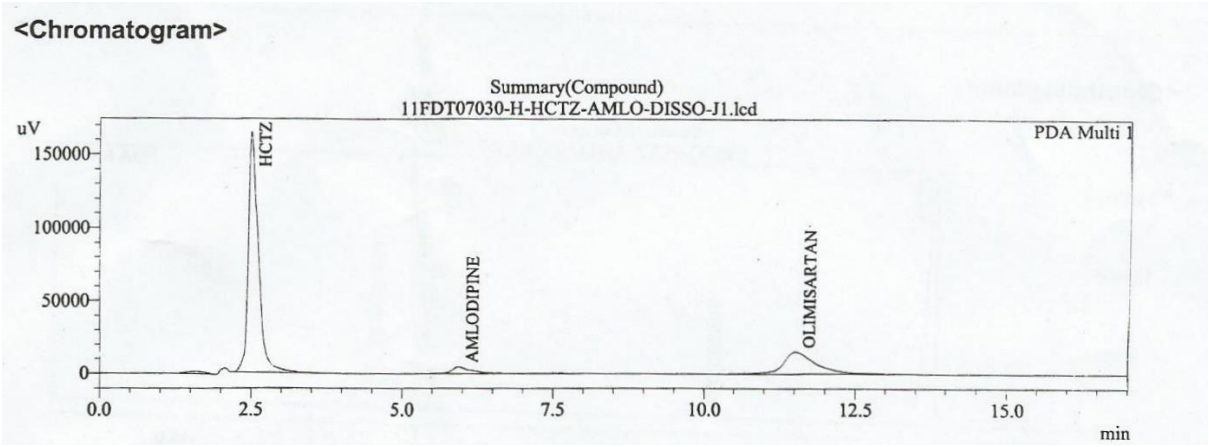


Figure 36: Dissolution for chromatogram for sample 1

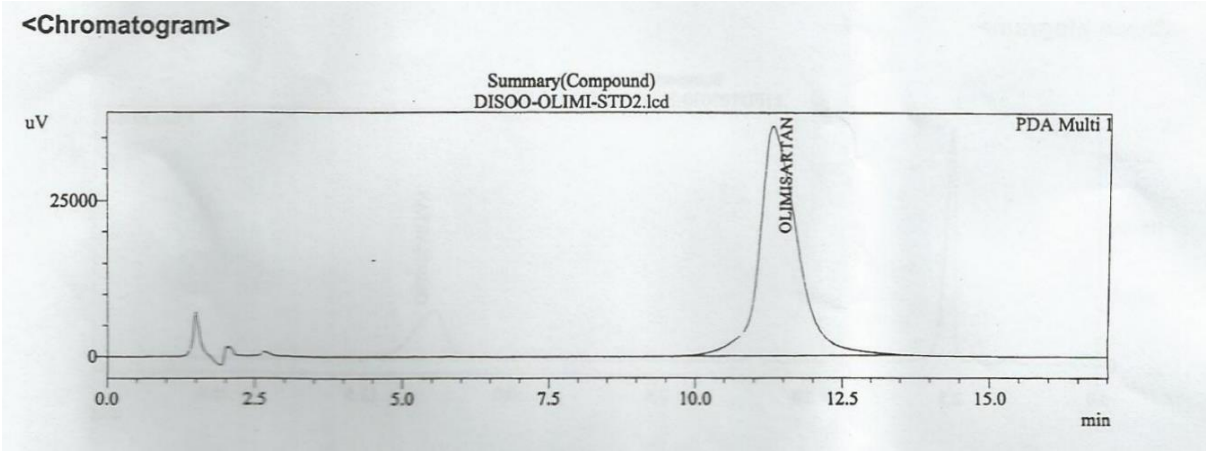


Figure 37: Chromatogram for dissolution standard 2

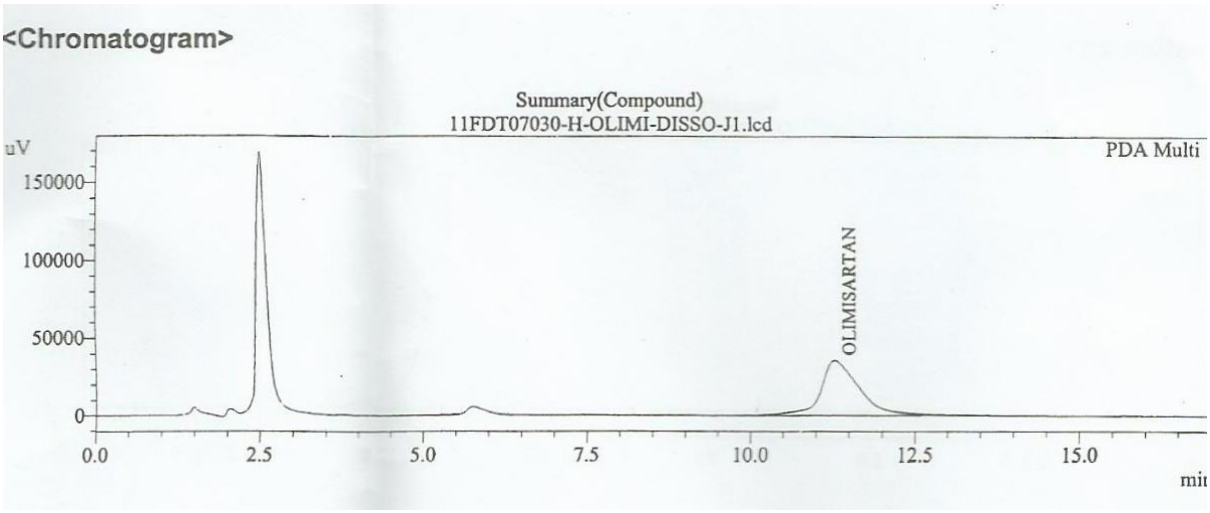


Figure 38: Chromatogram for dissolution sample 2

DISCUSSION:

The first formulation F-1 has been done with wet granulation method. It shows good flow properties but has poor hardness. So the concentration of the binder has been increased in the next formulation F-2 to improve hardness. Hardness is improved but disintegration time is very high (more than 15min). So, direct compression method has been opted in the next formulation F-3. In F-3 formulation also, flow problem is observed. Hence, diluent concentration is increased in the next formulation F-4. Even then, poor flow property is observed. Diluent concentration is further increased in the next formulation F-5 which showed an improved flow property but disintegration time is not satisfactory (14min). Disintegrant concentration is increased in the further formulations and various disintegrants are used for formulations F-6, F-7, F-8 to compare disintegration property of each and find out the optimum disintegrant. Compared to all formulations, F-6 showed enhanced disintegration power and drug release rate and possessed good flow property and hardness.

.

Stability studies of formulation:

Table 27: Assay

S.no	Temperature	Relative humidity	Time (days)	Olmesartan Medoxomil	Amlodipine Besylate	Hydrochlorot-hiazide
1.	25^0 c ± 2^0c	60% RH ± 5% RH	0	100.86	99.22	101.76
			30	99.92	98.34	100.12
2.	40^0 c ± 2^0c	75% RH ± 5% RH	0	100.86	99.22	101.76
			30	98.74	97.51	99.24

Table 28: Dissolution

s.no	Temperature	Relative humidity	Time (days)	Olmesartan Medoximil	Amlodipine Besylate	Hydrochlort-hiazide
1.	25^0 c ± 2^0c	60% RH ± 5% RH	0	99.76	97.12	98.37
			30	98.36	96.61	97.82
2.	40^0 c ± 2^0c	75% RH ± 5% RH	0	99.76	97.12	98.37
			30	97.22	95.12	96.10

SUMMARY

SUMMARY:

- In the present study an attempt was made to prepare triple drug combination of Amlodipine besylate, olmesartan medoximil and hydrochlorthiazide tablets for the treatment of hypertension.
- In the formulation developed by trials, F-1 and F-2 were made by wet granulation technique; there was a problem with the hardness and later with the disintegration time. So to improve the disintegration property, direct compression technique was adopted for the remaining trials.
- In the subsequent formulations F-3, F-4 and F-5, the diluent ratio with MCC PH 102 and pregelatinized starch were changed to improve the flow property and also the disintegration time.
- The formulation F-6 containing croscarmellose at its optimum concentration of 5% is compared with 5% SSG and 5% crospovidone and it was found that croscarmellose was a better disintegrant than the other two, as disintegration time and dissolution properties are better with the croscarmellose

The prepared tablets were evaluated for hardness, friability, weight variation, drug content uniformity, drug-excipient interaction, in vitro drug release and stability studies.

Among the various formulations prepared, Formulation F6 with croscarmellose sodium (5%) shows minimum disintegration time and improved dissolution properties compared to formulation F-1 to F-5. This is because of the dual action of wicking and swelling property of disintegrant.

CONCLUSION

CONCLUSION:

The present research was carried out to develop a novel, stable, triple drug combination of amlodipine besylate, olmesartan medoximil and hydrochlorthiazide. Combination of Amlodipine Besylate, olmesartan medoximil and hydrochlorthiazide are indicated for the successful treatment of hypertension.

Tablets were formulated by both wet granulation and direct compression methods using olmesartan medoximil, amlodipine besylate, hydrochlorthiazide and various excipients which include maize starch, pregelatinised starch, micro crystalline cellulose, PVP k30, isopropyl alcohol, MCC PH102, croscarmellose sodium, sodium starch glycolate, crospovidone, colloidal silicon dioxide an magnesium stearate. Results showed that the wet granulation method was a failure because of the disintegration and dissolution properties. Hence other formulations adopted a direct compression method and the optimized formulation is found using various evaluation properties. The optimized formulation F6 tablets were film coated in a conventional coating pan. Formulation characteristics such as content uniformity, hardness, friability were evaluated and found to be satisfactory.

In vitro dissolution studies of tablets were conducted for 30 minutes. Samples were analyzed by HPLC. The formulation (F-6) showed acceptable results and complied with the internal specifications for weight variation, thickness, hardness, friability, drug content and in vitro drug release.

Accelerated stability profile of tablets was found to be satisfactory. No sign of degradation was observed. Hence, it is finally concluded that, triple drug combination therapy for hypertension can be considered as one of the promising fixed drug dosage form.

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